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SCIENTIFIC AMERICAN REPORTS

SPECIAL EDITION ON DIET AND HEALTH

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EATING to LIVE

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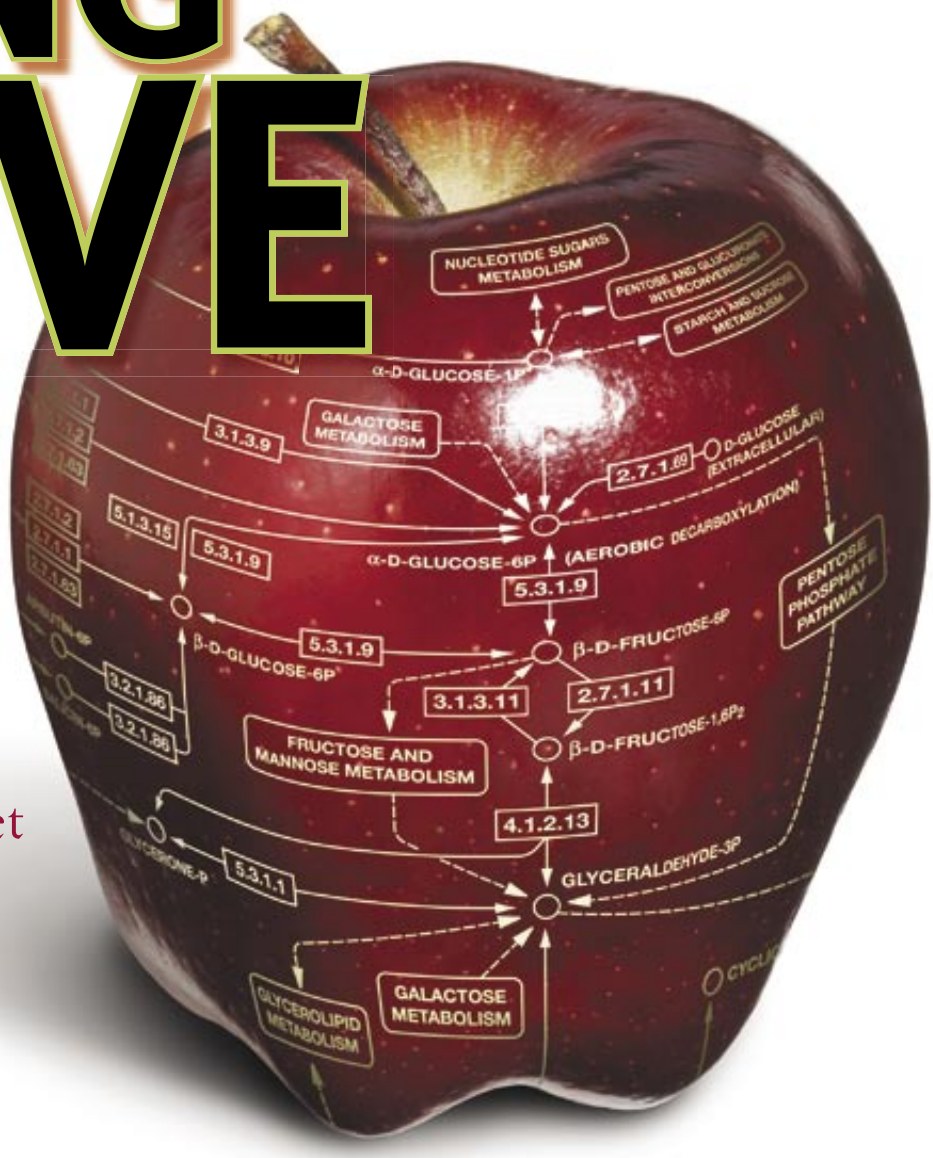
Edible Vaccines
Snacks that prevent disease

Better Food Pyramid
Makeover for the USDA guide

Birth of the Modern Diet
Why dessert comes after dinner



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SCIENTIFIC AMERICAN
REPORTS

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letter from the editor

Good Eating

EVEN 500 YEARS AGO people had some inkling that what we eat affects our well-being. "A good coke is halfe a physycyon," wrote Andrew Boorde in 1547 in *Breviary of Health*. Head chefs, or majordomos, seasoned their dishes with early ideas about diet and nutrition that still influence meals today, as Rachel Laudan explains in her article, "Birth of the Modern Diet," starting on page 4. We have been grappling with what food means for health ever since. In recent years, modern science has come to the table, gathering the many insights you'll find in this special issue.

Obviously, we need a certain minimum diet to survive. But overabundance is also a problem, as we learn in banner headline after headline about the detrimental effects on the cardiovascular system and other areas of the body. But is that so? In his article on page 76, W. Wayt Gibbs explores the question, "Obesity: An Overblown Epidemic?"

Also in the news a lot lately is the idea that cutting calories may prolong youthful vigor into old age. "Calorie Restriction and Aging," by Richard Weindruch, explains, beginning on page 54, how animals that consume one-third fewer calories in studies display greater vitality than animals fed a normal diet. If the regimen sounds punishing, don't despair. "The Serious Search for an Antiaging Pill," by Mark A. Lane, Donald K. Ingram and George S. Roth, offers hope for finding a drug that mimics the effects of calorie restriction. Turn to page 62.

Amounts are one factor, but what we eat is also a critical influence on our abilities to stay strong and active into the twilight years. Science has learned much since the "four food groups" that my mother nagged me about as a child. Starting on page 12, "Rebuilding the Food Pyramid," by Walter C. Willett and Meir J. Stampfer, reviews the latest research on creating a proper diet.

Last, as the holiday season is upon us, let us make a toast to another source of vital spirits. In "Drink to Your Health?" Arthur L. Klatsky tells us how small to moderate amounts of alcohol can lend cardiovascular benefits. The article begins on page 22. Cheers.

Mariette DiChristina
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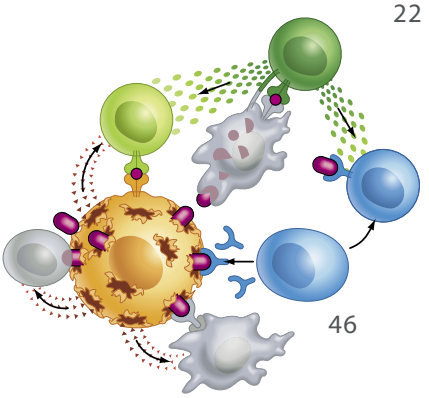

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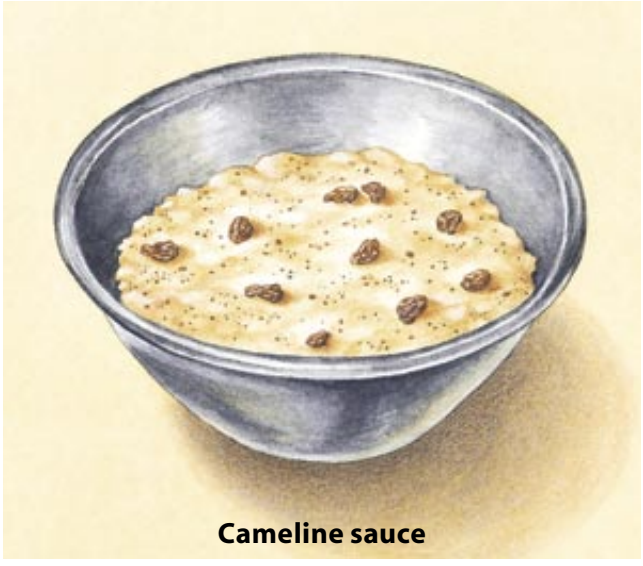
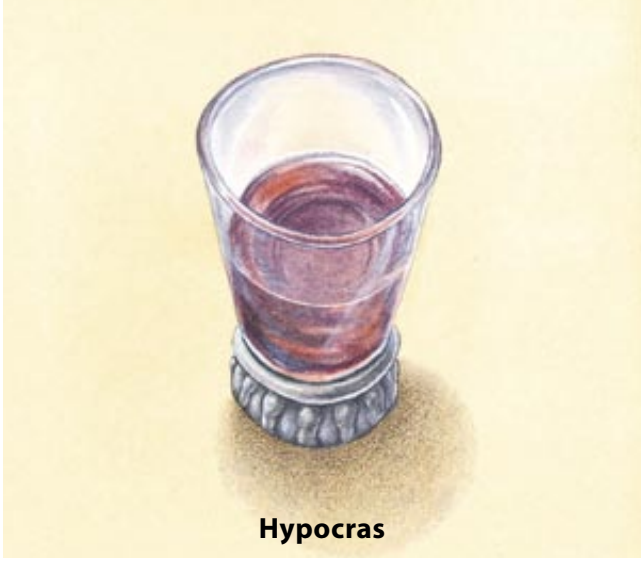
BEFORE 1650

Blancmange



Cameline sauce



Hypocras

SUMPTUOUS SPREAD from the 16th century might have included blancmange (a puree of rice and chicken) and a side dish of cameline sauce (made of crushed almonds, bread crumbs and spices moistened with sour grape juice), accompanied by mulled red wine, or hypocras. By the 17th century the foods looked more familiar to the modern eye: roast turkey, green salad with oil and vinegar dressing, and sparkling white wine.

Birth of Modern

Ever wonder why dessert is served after dinner?

By **Rachel Laudan**

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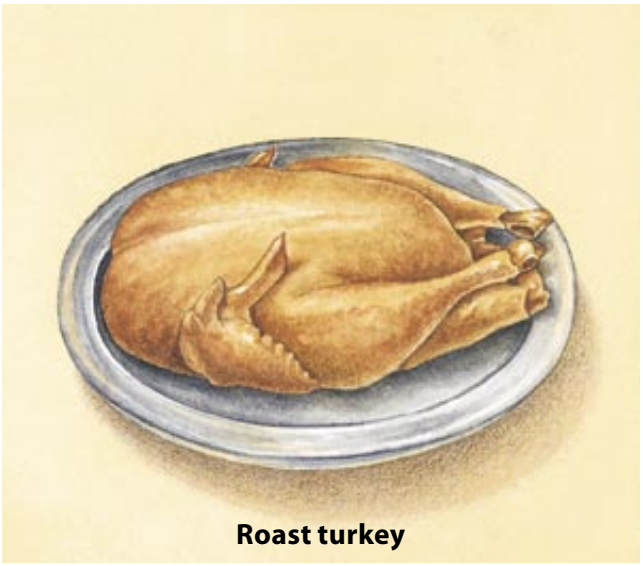
the Diet

The origins of modern Western cooking can be traced to ideas about diet and nutrition that arose during the 17th century

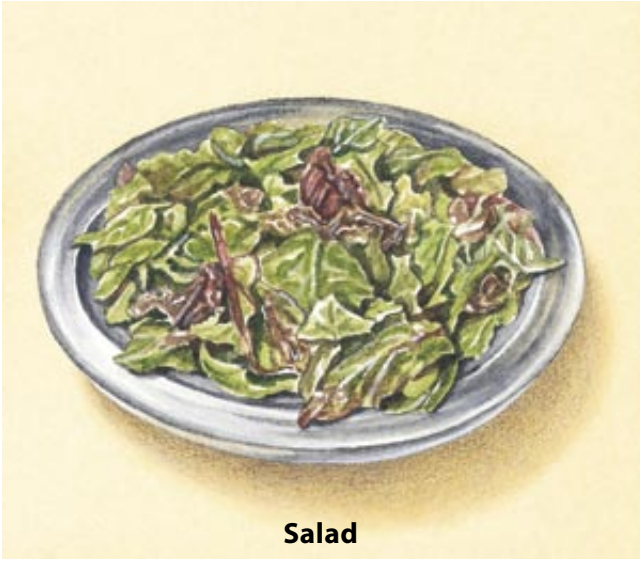
Were we to attend a 16th-century court banquet in France or England, the food would seem strange indeed to anyone accustomed to traditional Western cooking. Dishes might include blancmange—a thick puree of rice and chicken moistened with milk from ground almonds, then sprinkled with sugar and fried pork fat. Roast suckling pig might be accompanied by a cameline sauce, a side dish made of sour grape juice thickened with bread crumbs, ground raisins and crushed almonds, and spiced with cinnamon and cloves. Other offerings might consist of fava beans cooked in meat stock and sprinkled with chopped mint or quince paste, a sweetmeat of quinces and sugar or honey. And to wash it all down, we would probably drink hypocras, a mulled red wine seasoned with ground ginger, cinnamon, cloves and sugar.

Fast-forward 100 years, though, and the food would be reassuringly familiar. On the table might be beef bouillon, oysters, anchovies and a roast turkey with gravy. These dishes might be served alongside

AFTER 1650



Roast turkey



Salad

Sparkling wine

HEIDI NOLAND

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Eating healthy food was extremely important to people of earlier eras, perhaps even more so than it is today.

mushrooms cooked in cream and parsley, a green salad with a dressing of oil and vinegar, fresh pears, lemon sherbet, and sparkling white wine.

Before 1650, the elite classes throughout the Islamic and Christian worlds from Delhi to London shared pretty much the same diet: thick purees, lots of spices, sweet and sour sauces, cooked vegetables, and warmed wines. Sugar was ubiquitous as a seasoning in savory dishes. But in the middle of the 17th century, the northern European diet began to change. This new regimen relied on fewer spices, based its sauces on fats such as butter and olive oil, and incorporated raw fruits and vegetables. Sugar appeared only at the end of a meal.

What happened? Economic considerations cannot account for the difference: for the upper class, money was no object. For the poor, both meals would have been far out of reach. Well into the 19th century, they subsisted on vegetable soups and gruels with bread or porridge. Novel foodstuffs from the New World do not explain the shift in diet either, because with the exception of turkey, the dishes at the second banquet depended not on new ingredients but on new uses of long familiar ones. The clue to this transformation in eating habits between the 16th and 17th centuries must be sought instead in evolving ideas about diet and nutrition—which is to say, in the history of chemistry and medicine.

OVERVIEW

AS IDEAS ABOUT DIGESTION CHANGED, SO DID MENUS

- In the 16th century, digestion was thought to be a form of cooking. Food corresponded to the four Aristotelian elements—air, water, fire and earth—with the perfect meal being slightly warm and slightly moist.
- By the 17th century, digestion was believed to be a form of fermentation. Fat-based sauces, salt and fresh produce gained prominence among the elite classes, and sugar was relegated to dessert.
- Today almost everyone in the West can afford the diet that was reserved for the wealthy in the 17th century, but its heavy reliance on fats is partly to blame for modern obesity.

Medicine in the 16th Century

EATING healthy food was extremely important to people of earlier eras, perhaps even more so than it is today. Activity in the kitchen mattered so much because physicians had so few other options. To avoid resorting to unpleasant therapies such as purging or bloodletting, doctors carefully monitored their wealthy patients' daily habits: their emotional state, for example, or how much sleep, exercise and fresh air they got. Most crucially, doctors advised their patients on the food and drink they should consume. Every court had a bevy of physicians who were schooled in the physiology of digestion, the nutritive properties of foodstuffs and the nature of a healthy meal. Offering dietary advice to their affluent patrons was a major part of their work.

The actual task of transforming abstract dietary theory into dishes appropriate for the courtly table fell to the head chefs, or majordomos, as they were often called. In a popular medical text written in 1547, *Breviary of Health*, author Andrew Boorde noted, "A good coke is halfe a physycyon." Sixteenth-century cooks, physicians and their patrons shared a common notion of diet and nutrition that can be traced to classical antiquity. First formulated around 400 B.C. as part of the Hippocratic Collection, the ideas were systematized by the great Roman doctor Galen in the early second century A.D. After the collapse of classical civilization, Islamic intellectuals eagerly took up these notions (along with many other scientific theories of the ancient world).

By the 12th century, European scholars had translated key Arabic texts into Latin; teachers at the major medical schools, such as Montpellier in the south of France, relied extensively on these texts. In the late 15th century, experts began translating newly discovered Greek manuscripts as well as retranslating known texts. These documents formed the basis of a host of popular manuals and mnemonic jingles. Particularly well liked were the numerous vernacular variations on a Latin poem, the *Regimen Sanitatis Salernitanum*, apparently composed around the end of the 11th century but still widely circulated in the 16th and even 17th centuries:

Peaches, apples, pears, milk,
cheese, and salted meat,
Deer, hare, goat, and veal,
These engender black bile and
are enemies of the sick

The prevailing dietary wisdom of the 16th century, as presented in these medical guidebooks, relied on two assumptions: first, that the process of digesting foods was actually a form of cooking. Indeed, cooking stood as the basic metaphor for the systems that sustained all life. Seeds were cooked into plants; when the plants appeared above the ground, the heat of the sun cooked them into ripe fruits and grains. If humans gathered these foodstuffs, they could cook them further to create edible dishes. Finally, the internal heat of

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the body turned the food into blood. The body then expelled as feces what was not digestible. Excrement joined putrefying dead animals and plants to begin the life cycle again.

The second assumption about food and health in this scenario involved maintaining a proper equilibrium of bodily fluids by eating a suitably balanced diet. Doctors and chefs of the time believed that four fluids, or humors, circulated in the body: blood, phlegm, yellow bile and black bile. These humors corresponded to the four Aristotelian elements—air, water, fire and earth. Because blood was hot and moist, it corresponded to air; phlegm was cold and moist and thus resembled water; yellow bile was hot and dry, similar to fire; black bile was cold and dry, connected to earth.

Ideally, the human body was slightly warm and slightly moist, although in practice the exact balance varied from individual to individual, depending on variables such as age, sex and geographic location. Older people were believed to be colder and drier than younger ones; menstruating women colder and wetter than men; southern Europeans more hot-blooded than their neighbors to the north. The perfect meal, like the perfect human temperament, was slightly warm and slightly moist, but combinations away from this center could be used as mild dietary correctives to warm and moisten the elderly, dry out the moister sex, and calm down the southerner or perk up the northerner.

The majordomo, then, had the challenge of selecting and preparing meals adjusted to the temperament of the eater. The properties of any given food item were common knowledge: pepper, for example, was hot and dry in the third degree, and vinegar was cold and wet in the second degree. Root vegetables such as turnips were by nature earthy—dry and cold—and thus better left to peasants. If chefs should decide to prepare them, however, they would make sure to stew them, thereby adding warmth and moisture. In contrast, chard, marrow (a watery, squashlike vegetable) and especially onions were very wet and had to be fried.

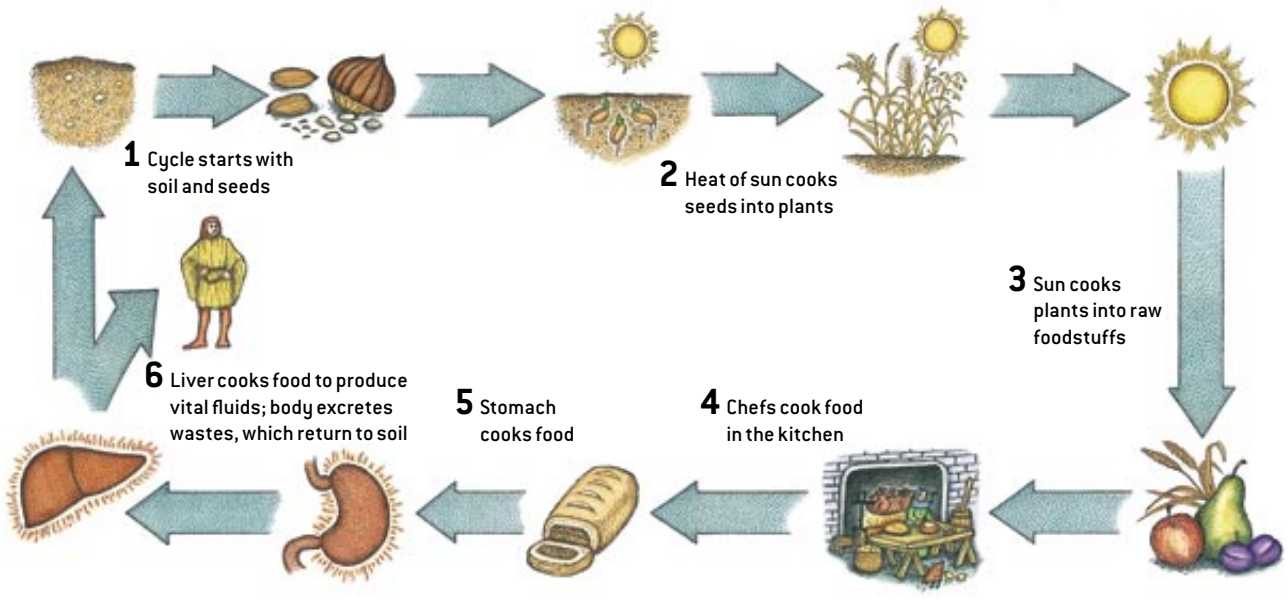
Other foods were completely unacceptable: Guy Patin, a doctor at the University of Paris and author of *Treatise on the Conservation of Health,* published in 1632, cautioned that mushrooms, being cold and wet, should be avoided entirely. Melons and other fresh fruit were not much better, being very moist and liable to putrefy. In general, though, cooking not only helped achieve proper culinary balance—dry foods were boiled, wet foods fried or roasted—but the process also, in effect, partially predigested the foods, making them easier for the body to assimilate.

According to these medical theories, the blancmange on our 16th-century table was close to perfect. The wise chef had combined chicken, rice and almond milk, all slightly warm and moist, and the sugar on top—also warm and moist—was the crowning touch. The naturally moist suckling pig had been roasted. The cameline sauce balanced cool, moist vinegar with the warmth of raisins and hot, dry spices. The chef was careful not to serve quinces and grapes fresh, and hence dangerously cold and moist, but instead offered them dried or cooked with added sugar (in the quince paste).

Health experts viewed wine with a meal as an ideal nutrient—provided, of course, that diners did not drink to excess. *The Book of Wine,* written around 1310, printed in 1478 and widely attributed to Arnald of Villanova (a leading medical writer and physician to

THE COSMIC CULINARY CYCLE BEFORE 1650

... in which cooking was believed to be the central process of life.


1 Cycle starts with soil and seeds
2 Heat of sun cooks seeds into plants
3 Sun cooks plants into raw foodstuffs
4 Chefs cook food in the kitchen
5 Stomach cooks food
6 Liver cooks food to produce vital fluids; body excretes wastes, which return to soil

PATRICIA J. WYNNE

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Chemists discovered that edible substances always separated into three parts when heated.

James II of Aragon), had only high praise for the beverage: besides being good for flatulence and infertility, wine "fortifies the brain and the natural strength … causes foods to be digested and produces good blood." Even so, because red wine tended to be cold and dry, chefs often served it warm with added sugar and spices, creating hypocras. With these options before them, the members of the 16th-century court could rest assured that they were getting a healthy meal.

17th-Century Cooking

BY THE MIDDLE of the 17th century, however, physicians of a quite different persuasion began to join the courts of northern Europe. These scholars derived their ideas from Paracelsus, an itinerant doctor from Germany who, in the 1520s, began to mock the structure of classical medicine. Paracelsus's abrasive personality and radical religious beliefs gave him a dreadful reputation, so few physicians admitted to this heritage. But acknowledged or not, the link was clear: these court doctors argued, as Paracelsus had, that the idea of a cosmic life cycle based on cooking and the Aristotelian elements was wrong and had to be revised.

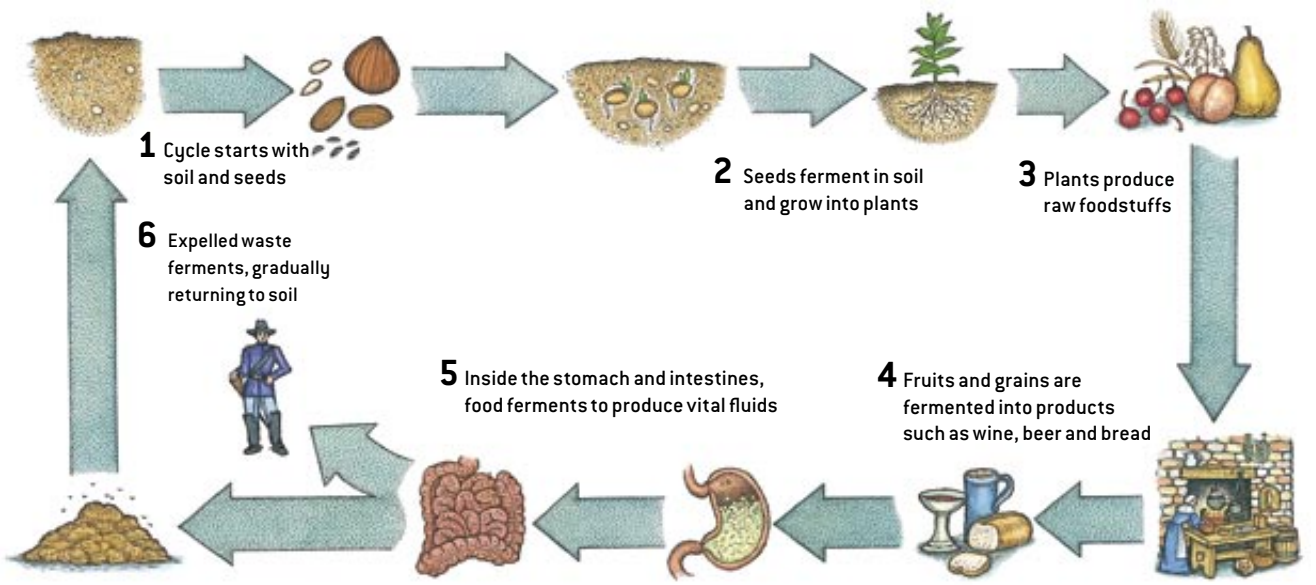
Historians of science still debate the causes of this shift, but the technology of distillation seems to have contributed to it. As the practice became more important from the late Middle Ages on, chemists experimented with heating a great variety of natural substances, many of them edible, such as fennel, nutmeg and cloves. They noted that in every case the original material separated into three parts: a volatile, or "spirituous," fluid; an oily substance; and a solid residue.

Drawing on such observations, these chemists proposed three new elements in place of Aristotle's four: mercury (the essence of the vaporous fluids; not related to the toxic chemical of the same name), sulfur (the essence of the oily substances; again, unrelated to the chemical) and salt (the essence of the solids; not the same as modern table salt). In such a scheme, salt dictated the taste and consistency of foods. Mercury was the source of smells and aromas. Sulfur, or oil, carried the properties of moistness and sweetness; it also bound together the other two, usually antagonistic, elements.

Physicians of this era also believed that digestion involved fermentation rather than cooking, and they began to investigate the familiar yet mysterious process more closely. Because fermentation included gentle heat and the production of vapors, it seemed to resemble (or was possibly the same as) putrefaction, distillation, and the interaction of acids and salts. Vapors, spirits or airs (soon to be dubbed "gases" by Dutch

THE COSMIC CULINARY CYCLE AFTER 1650

… in which fermentation was believed to be the central process of life.


1 Cycle starts with soil and seeds
2 Seeds ferment in soil and grow into plants
3 Plants produce raw foodstuffs
4 Fruits and grains are fermented into products such as wine, beer and bread
5 Inside the stomach and intestines, food ferments to produce vital fluids
6 Expelled waste ferments, gradually returning to soil

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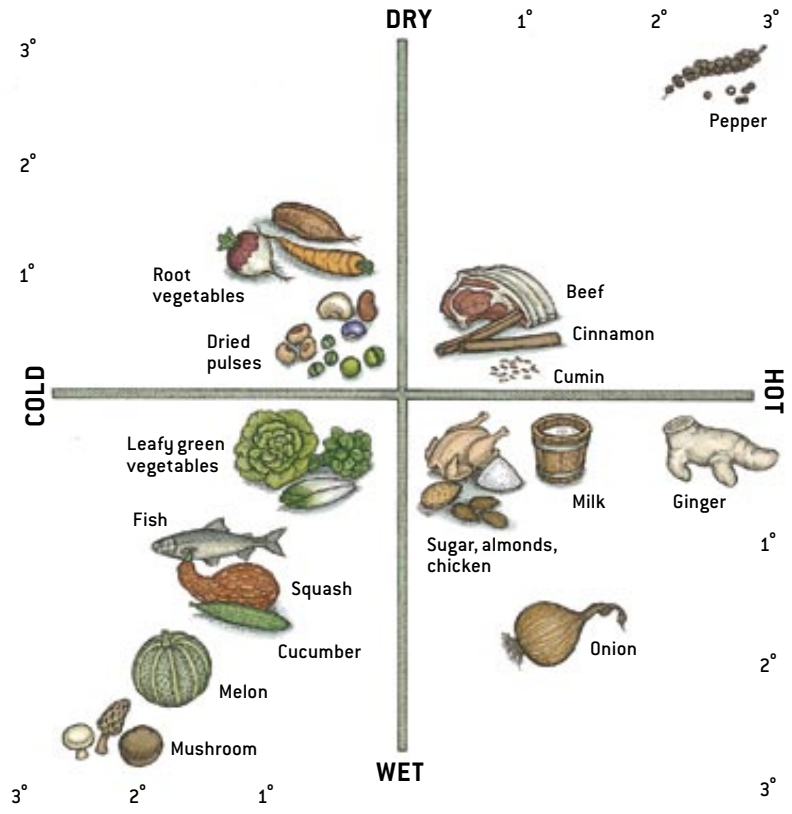
16TH-CENTURY CLASSIFICATION SYSTEM

... in which foods were assigned degrees of heat, coldness, wetness and dryness.



scientist and mystic Johannes Baptista van Helmont) excited chemists of the time, as they appeared to be the very essence of the substance from which they originated.

Several prominent physicians of the 17th century advocated this new understanding of digestion, among them van Helmont, Franciscus Sylvius, a physician at the University of Leiden, and Thomas Willis, then the best-known doctor in England and a founding member of the Royal Society of London. According to this view, digestion involved the fermenting, rather than the cooking, of foodstuffs. Gastric juices, considered acid and sharp, acted on foods to turn them into a white, milky fluid, which then mixed with alkaline bile in the digestive tract. The mixture fermented and bubbled, producing a salty substance that the body could transform into blood and other fluids.

Like their 16th-century predecessors, these later physicians presented a cosmic cycle of life that reflected their view of digestion. Seeds became plants as a result of the "ferments of the earth," in the words of John Evelyn, a keen horticulturist who spoke before the Royal Society in 1675. Fermentation turned grains and fruits into bread, beer and wine, which the digestive system could ferment further. Putrefaction of waste material started the cycle all over again. "Vegetable putrefaction resembles very much Animal Digestion," stated John Arbuthnot, member of the Royal Society and physician to Queen Anne, in a popular handbook on foodstuffs that appeared in 1732. The cosmos was still a kitchen but was now equipped with brewers' vats, and the human body held miniature copies of that equipment.

These changes in the understanding of the digestive process put 17th-century chefs on guard. Alert cooks seized the opportunity to establish their good reputations by thinking up dishes that were healthful by the new standards—and, of course, also tasty. For instance, chefs welcomed oysters, anchovies, green vegetables, mushrooms and fruits because they fermented so readily and thus did not need complicated preparation in the kitchen to be predigested. As cooks began to incorporate fresh produce into many of their dishes, horticulture and botanical gardens became the rage. Scientists and scholarly gentlemen exchanged seeds, translated gardening books and developed hothouses for tender vegetables. They began cultivating mushrooms on beds of putrefying dung. In England, the well-to-do put even such previously distasteful dishes as eggplant on their tables.

The First Restaurants

SUBSTANCES rich in oil, such as butter, lard or olive oil, all with the useful property of binding the components of salt and mercury, became the basis of a variety of sauces. They were combined with ingredients containing the element salt, such as flour and table salt, and others high in mercury, such as vinegar, wine, spirits, and essences of meat or fish. The first recipe for roux, a combination of fat and flour moistened with wine or stock to produce a single deli-

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RACHEL LAUDAN received her doctorate in history and philosophy of science from the University of London. During her academic career she held appointments at Carnegie Mellon University, Virginia Polytechnic Institute and State University, the University of Hawaii, the Massachusetts Institute of Technology and the Institute for Advanced Study in Princeton, N.J. Among her many publications on the history of science is *From Mineralogy to Geology: The Foundations of a Science 1650–1830* (University of Chicago Press, 1987). For the past decade she has lived in Mexico and written about the history and politics of food. She is the winner of the Jane Grigson prize for food scholarship of the Julia Child Cookbook Awards and the Sophie Coe Prize for Food History of the Oxford Symposium on Food & Cookery. She is currently finishing a new book, *Cuisine and Empire: A Global History of Cooking and Its Consequences.*

PATRICIA J. WYNNE

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Sugar, formerly a panacea, came in for rough treatment at the hands of the chemical physicians.

cious taste, appeared in the cookbook *The French Chef,* written in 1651 by François Pierre de la Varenne. Salads, which combined oil-based dressings and readily digestible greens, also became quite fashionable. (Evelyn promoted vinaigrette salad dressing in his *Acetaria: A Discourse of Sallets,* published in 1699.)

As fruits, herbs and vegetables assumed a more prominent place in the main meal, sugar, formerly lauded as a panacea, came in for rough treatment at the hands of the chemical physicians. Some wanted to banish it altogether. "Under its whiteness," hissed Joseph Duchesne, physician to Henry IV of France, in 1606, "sugar hides a great blackness"—doctors knew that it blackened the teeth—"and under its sweetness a very great acrimony, such that it equals agua fortis [nitric acid]."

British physician Willis, who had noticed the sugary urine of patients suffering from what doctors later termed diabetes, concurred: "Sugar, distilled by itself, yields a liquor scarcely inferior to aqua fortis.... Therefore it is very probable that mixing sugar with almost all our food, and taken to so great a degree, from its daily use, renders the blood and humours salt and acrid; and consequently scorbutic."

The moral was clear: sugar was dangerous, perhaps even a poison. Such dire warnings would surely have given any chef second thoughts about sprinkling it over the main dishes of the meal, leaving the diner no choice but to eat it. Thus, sugar moved to the periphery of the menu, served only in desserts, which were prepared in a separate kitchen. Sugar became the subject of a distinct genre of books dedicated to its decorative, not medical, properties.

Physicians regarded alcoholic spirits and other distilled essences as useful medicines. They and their patients, though, considered a cordial or an eau-de-vie fine for the occasional sip but too strong for everyday use. Less powerful extractions, made from nutritive foods such as meats that had been concentrated by boiling or fermenting, could be more easily digested. Sometimes the concentrated goodness of a food even showed up as desirable gas bubbles that nourished the brain. Sparkling mineral waters gained immense popularity as spas opened across Europe. At the ta-

Typical Pre-17th-Century Recipes

Cameline sauce

"To make an excellent cameline sauce, take skinned almonds and pound and strain them; take raisins, cinnamon, cloves and a little crumb of bread and pound everything together, and moisten with verjuice*; and it is done."
**sour juice of unripe grapes*

Blancmange

"Take cooked breasts of chicken and put them on a table and shred them into the finest fibers you can. Then wash the rice and dry it, and make it into flour, and put it through a sieve; then moisten this rice flour with goat's, sheep's or almond milk, and boil it in a well-washed and clean pan; and when it begins to boil, add those shredded breasts, with white sugar and fried white pork fat; and keep it away from the smoke, and let it boil gently without excessive fire, so that it becomes as thick as the rice should be. And when you serve it, top it with crushed or pounded sugar, and fried pork fat."

Hypocras

"To make a lot of good hypocras, take an once of cinamonde, known as long tube cinnamon, a knob of ginger, and an equal amount of galangal,* pounded well together, and then take a livre of good sugar; pound this all together and moisten it with a gallon of the best Beaune wine you can get; and let it steep for an hour or two. Then strain it through a cloth bag several times so it will be very clear."
**a root in the ginger family*

SOURCE: *THE MEDIEVAL KITCHEN: RECIPES FROM FRANCE AND ITALY,* UNIVERSITY OF CHICAGO PRESS, 1998

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The Three Principles

... by which foods were classified in the late 17th century.

The Mercury Principle
Makes food volatile or gaseous, gives it smell (vinegar, wine, meat essence)

The Sulfur Principle
Makes food oily, binds foods high in salt and mercury (oil, butter, lard)

The Salt Principle
Gives food taste (salt, flour)

PATRICIA J. WYNNE

ble, hot and spicy hypocras yielded to cool wines, even to sparkling champagne, which was most likely first produced in the late 17th century.

Chefs made essences of meat or fish from the "musculous Flesh, which is of all [parts of the animal] the most nourishing, that which produces the best juice," and then served this healthy fare in the form of stock, bouillon or jellies made from these liquids. Land animals had more nutritious juices than fish or birds did, and of the land animals, beef produced the most restorative ones. By 1733 Vincent la Chapelle, a French chef who worked for the earl of Chesterfield in England, had a variety of recipes for delicately garnished beef bouillon in his book *The Modern Cook,* which was quickly translated into French. Before long, entrepreneurs saw an opportunity in this new cuisine, selling "restaurants"—which is French for "restoratives"—to those who could not afford their own chefs.

Eventually Europe's middle classes emulated the aristocracy, developing a taste not only for restaurants but for all the new cuisine. Such foods seemed to offer a certain refinement, not just in the sense of good taste but also in a chemical sense, as the meals represented the most enhanced form of food. As the authors of the gastronomic treatise *The Gifts of Comus,* published in Paris in 1739, put it: "Modern cookery is a kind of chemistry. The cook's science consists today of analyzing, digesting, and extracting the quintessence of foods, drawing out the light and nourishing juices, mingling and blending them together."

This new diet gradually spread across Europe as it simultaneously made its way down the social scale. By the mid- to late 19th century it had become the standard for the English- and French-speaking worlds in Europe, the U.S., Canada and Australia. Other regions, however—the Islamic world and Spanish-speaking parts of the Americas, for example—remained isolated from the chemistry derived from Paracelsus and adopted neither the dietary theory nor the resultant cuisine. (The modern curries of India and moles of Mexico, for instance, resemble the cuisine of pre-Paracelsian northern Europe.)

The Western cuisine born in the 17th century long outlived the dietary theory that inspired it. By the end of the 18th century, chemists and physicians had embarked on the research that was to lead to the modern theories of the role of calories, carbohydrates, proteins, vitamins and minerals in the biochemical processes of digestion. Notably, during the 19th and early 20th centuries, when most of these studies were carried out, nutritionists focused on developing a cheap but adequate diet for factory workers, soldiers and other less affluent people. The shift of emphasis in the medical community from the rich to the poor, though, meant that chefs catering to the well-heeled continued to develop Western cuisine along the lines established in the 17th century.

Now that almost everyone in the West can afford the cuisine formerly restricted to the wealthy, we have come to realize that its dietary foundations are a mixed blessing. Although fresh fruit and vegetables score high marks, the centrality of fat in our diets (a result of the importance given to meat and fat-based sauces) is blamed for the high rates of obesity in most developed nations. In response, everyone from physicians to chefs has returned attention to the age-old problem of developing a new cuisine, at once delicious and in line with the latest findings in physiology and nutrition. SA

MORE TO EXPLORE

The French Paracelsians: The Chemical Challenge to Medical and Scientific Tradition in Early Modern France. Allen G. Debus. Cambridge University Press, 1991.

Acquired Taste: The French Origins of Modern Cooking. T. Sarah Peterson. Cornell University Press, 1994.

The Art of Cookery in the Middle Ages. Terrence Scully. Boydell Press, 1995.

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Rebuilding the Food Pyramid

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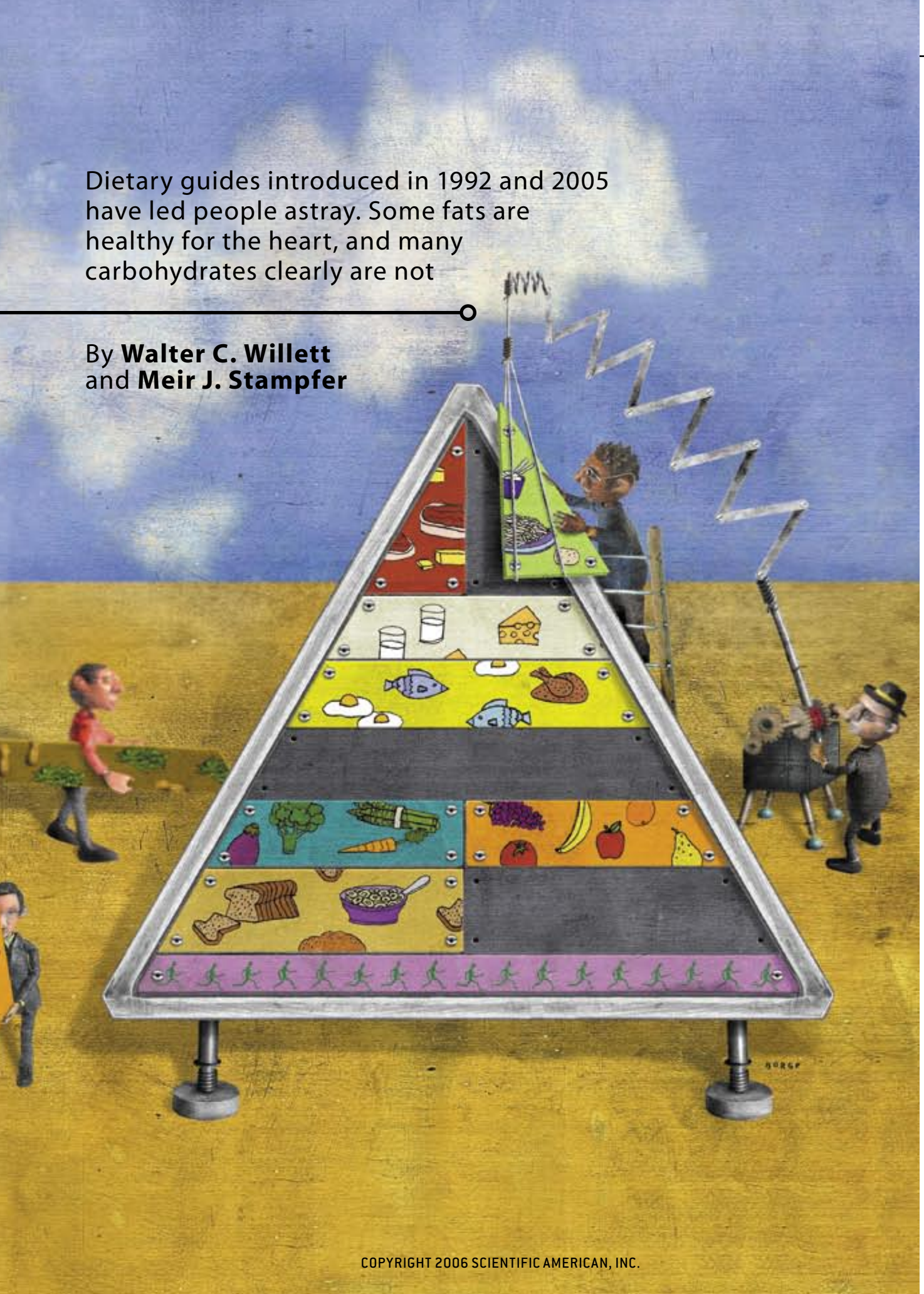
Dietary guides introduced in 1992 and 2005 have led people astray. Some fats are healthy for the heart, and many carbohydrates clearly are not

By **Walter C. Willett** and **Meir J. Stampfer**



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In 2005 the U.S. Department of Agriculture officially released its newest Food Guide Pyramid, which was intended to help the American public make dietary choices that would maintain good health and reduce the risk of chronic disease.

The new pyramid attempts to provide individualized advice based on a person's age, gender and level of physical activity. It focuses on the consumption of grains, meat and beans, milk, vegetables, fruit, and oils.

The 2005 pyramid replaced a 1992 USDA pyramid that differed from it in several respects. The new pyramid provides more emphasis on whole grains and physical activity. It does not, however, solve all the problems associated with its predecessor, because it still places too much emphasis on grains and milk and does not sufficiently emphasize the adverse effects of some types of fat. Unlike the old pyramid's graphic representation, which showed the proportions of various foods that should be consumed as stacked layers of different sizes, the 2005 pyramid conveys no information about nutrition; it simply shows a figure ascending a rainbow-colored staircase [*see box on page 17*].

We have drawn up a revised pyramid that better reflects the current evidence regarding the relation between diet and health. Studies indicate that adherence to the recommendations in our revised pyramid can significantly reduce the risk of cardiovascular disease for both men and women.

The Old Food Pyramid

THE USE OF IMAGES to promote dietary advice goes back nearly a century in the U.S. The recommendations embodied in the 1992 pyramid were widely adopted, and the image became an icon. The basic advice was that people should minimize their consumption of fats and oils but should eat six to 11 servings a day of foods rich in complex carbohydrates—bread, cereal, rice, pasta and so on. The food pyramid also recommended generous amounts of vegetables (including potatoes, another plentiful source of complex carbohydrates), fruit and dairy products, and at least two servings a day from the meat and beans group, which lumped together red meat with poultry, fish, nuts, legumes and eggs.

Even when the pyramid was being developed, though, nutritionists had long known that some types of fat are essential to health and can reduce the risk of cardiovascular disease. Furthermore, scientists had found little evidence that a high intake of carbohydrates is beneficial. After 1992 more and more research showed that the USDA pyramid was grossly flawed. By promoting the consumption of all complex carbohydrates and eschewing all fats and oils, the pyramid provided misleading guidance. In short, not all fats are bad for you, and by no means are all complex carbohydrates good for you.

How did the original USDA pyramid go so wrong? In part, nutritionists fell victim to a desire to simplify their dietary recommendations. Researchers had known for decades that saturated fat—found in abundance in red meat and dairy products—raises cholesterol levels in the blood. High cholesterol levels, in turn, are associated with a high risk of coronary heart disease (heart attacks and other ailments caused by the blockage of the arteries to the heart). In the 1960s controlled feeding studies, in which the participants ate carefully prescribed diets for several weeks, substantiated that saturated fat increases cholesterol levels. But the studies also showed that polyunsaturated fat—found in vegetable oils and fish—reduces cholesterol. Thus, dietary advice during the 1960s and 1970s emphasized the replacement of saturated fat with polyunsaturated fat, not total fat reduction.

The notion that fat in general is to be avoided stems mainly from observations that affluent Western countries have both high intakes of fat and high rates of coronary heart disease. This correlation, however, is limited to saturated fat. Societies in which people eat relatively large portions of monounsaturated and polyunsaturated fat tend to have lower rates of heart disease [*see box on page 21*].

On the Greek island of Crete, for example, the traditional diet contained much olive oil (a rich source of monounsaturated fat) and fish (a source of polyunsaturated fat). Although fat constituted 40 percent of the calories in this diet, the rate of heart disease for those who followed it was lower than the rate for those who followed the traditional diet of Japan, in which fat made up only 8 to 10 percent of the calories. Furthermore, international comparisons can be misleading: many negative influences on health, such as smoking, physical inactivity and high amounts of body fat, are also correlated with Western affluence.

Unfortunately, many nutritionists decided it would be too difficult to educate the public about these subtleties. Instead they put out a clear, simple message: "Fat is bad." Because saturated fat represents about 40 percent of all fat consumed in the U.S., the rationale of the USDA was that advocating a

RICHARD BORGE (*preceding pages*)

OVERVIEW
THE FOOD GUIDE PYRAMID

- The U.S. Department of Agriculture's 1992 Food Guide Pyramid recommended that people minimize fats but eat plenty of carbohydrate-rich foods such as bread, cereal, rice and pasta. The goal was to reduce the consumption of saturated fat, which raises cholesterol levels.
- A revised USDA pyramid unveiled in 2005 places more emphasis on whole grains and exercise. But it pays insufficient attention to the dangers of sugar and some types of fat and neglects the benefits of healthier oils.
- Nutritionists are now proposing a new food pyramid that encourages the consumption of healthy fats and whole grain foods but recommends minimizing refined carbohydrates, butter and red meat.

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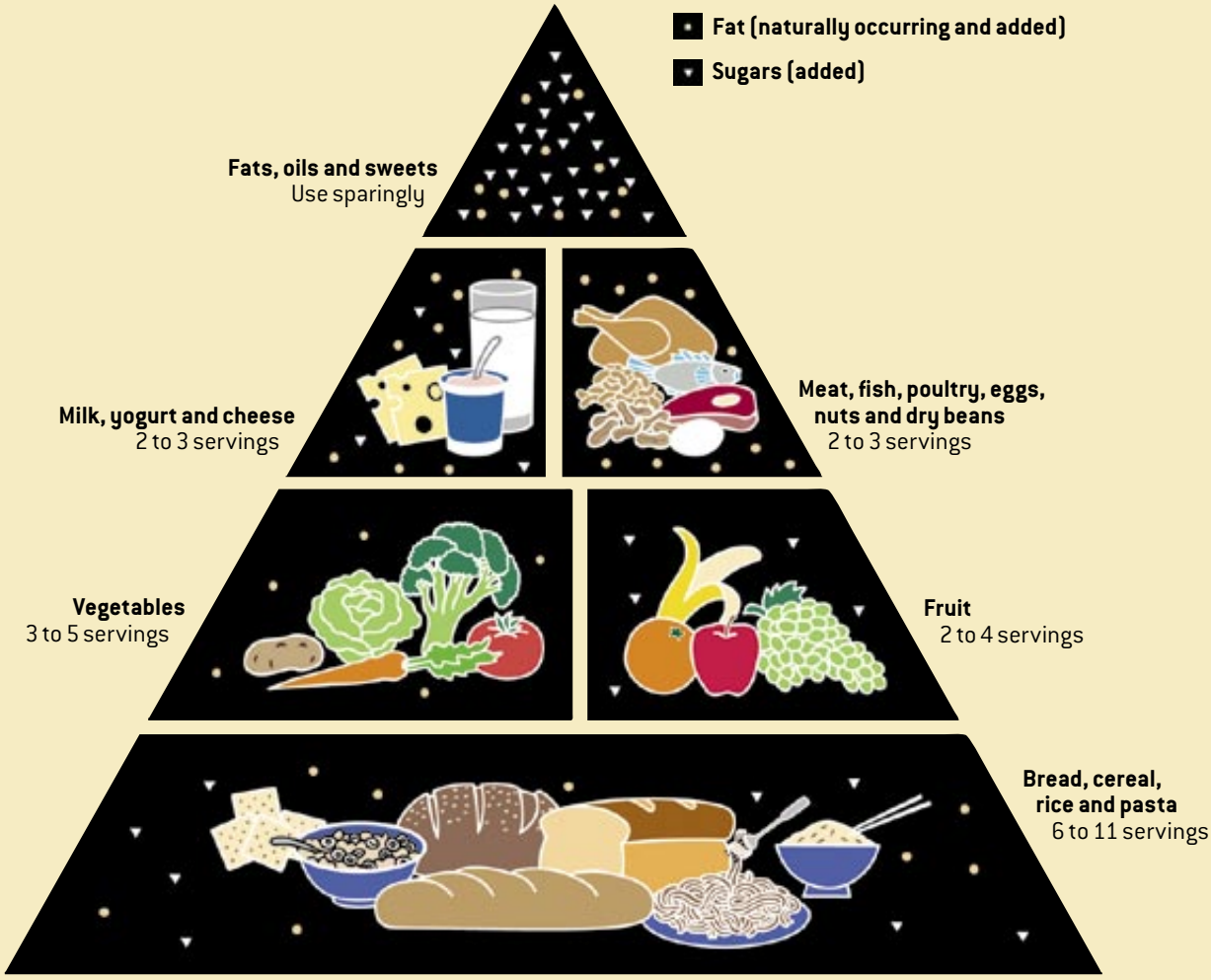
low-fat diet would naturally reduce the intake of saturated fat. This recommendation was soon reinforced by the food industry, which began selling cookies, chips and other products that were low in fat but often high in sweeteners such as sucrose and high-fructose corn syrup.

When the original food pyramid was being developed, the typical American got about 40 percent of his or her calories from fat, about 15 percent from protein and about 45 percent from carbohydrates. Nutritionists did not want to suggest eating more protein, because many sources of protein (red meat, for example) are also heavy in saturated fat. So the "Fat is bad" mantra led to the corollary "Carbs are good." Dietary guidelines from the American Heart Association and other groups recommended that people get at least half their calories from carbohydrates and no more than 30 percent from fat. This 30 percent limit has become so entrenched among nutritionists that even the sophisticated observer could be forgiven for thinking that many studies must show that individuals with that level of fat intake enjoy better health than those with higher levels. But no study has demonstrated long-term health benefits that can be directly attributed to a low-fat diet. The 30 percent limit on fat was essentially drawn from thin air.

The wisdom of this direction became even more questionable after researchers found that the two main cholesterol-carrying chemicals—low-density lipoprotein (LDL), popularly known as "bad cholesterol," and high-density lipoprotein (HDL), known as "good cholesterol"—have very different effects on the risk of coronary heart disease. Increasing the ratio of LDL to HDL in the blood raises the risk, whereas decreasing the ratio lowers it. By the early 1990s controlled feeding studies had shown that when a person replaces calories from saturated fat with an equal amount of

1992 FOOD PYRAMID

Conceived by the U.S. Department of Agriculture, this graphic representation of nutritional advice was intended to convey the message "Fat is bad" and its corollary "Carbs are good." These sweeping statements have since been questioned.



For information on the amount of food that counts as one serving, visit www.fns.usda.gov/tn/Resources/Nibbles/servingsize_poster.pdf

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calories from carbohydrates the levels of LDL and total cholesterol fall, but the level of HDL also falls. Because the ratio of LDL to HDL does not change, there is only a small reduction in the person's risk of heart disease. Moreover, the switch to carbohydrates boosts the blood levels of triglycerides, the component molecules of fat, probably because of effects on the body's endocrine system. High triglyceride levels are also associated with a high risk of heart disease.

The effects are more grievous when a person switches from either monounsaturated or polyunsaturated fat to carbohydrates. LDL levels rise and HDL levels drop, making the cholesterol ratio worse. In contrast, replacing saturated fat with either monounsaturated or polyunsaturated fat improves this ratio and would be expected to reduce heart disease. The only fats that are significantly more deleterious than carbohydrates are the trans-unsaturated fatty acids; these are produced by the partial hydrogenation of liquid vegetable oil, which causes it to solidify. Found in many margarines, baked goods and fried foods, trans fats are uniquely bad for you because they raise LDL and triglycerides while reducing HDL.

The New Food Pyramid

THE 2005 PYRAMID provided a unique opportunity to draw on more than a dozen years of advances in nutritional science. Although the new pyramid improved on the 1992 version in several ways, overall it was a major disappointment to many nutrition experts. A big change is that the basic image no longer conveys any information about diet—the figure climbing the pyramid promotes physical activity, but to get any dietary advice, one must visit the Web site www.mypyramid.gov and make selections for age, gender and current level of physical activity. Thus, a marvelous opportunity to provide succinct dietary advice to consumers was squandered, and the impact of the new pyramid on diet most likely will be modest compared with what it might have been.

The dietary advice that accompanies the pyramid, for those who navigate the Web site, represents some clear improvements over the 1992 version. Whole grains are emphasized more; the distinction between types of fats is clearer; and healthier choices for protein sources are emphasized. But these are only incremental changes and do not fully reflect the best dietary advice available today.

The Big Picture

TO EVALUATE FULLY the health effects of diet, one must look beyond cholesterol ratios and triglyceride levels. The foods we eat can cause heart disease through many other pathways, including raising blood pressure or boosting the tendency of blood to clot. And other foods can prevent heart disease in surprising ways; for instance, omega-3 fatty acids (found in fish and some plant oils) can reduce the likelihood of ventricular fibrillation, a heart rhythm disturbance that causes sudden death.

The ideal method for assessing all these adverse and beneficial effects would be to conduct large-scale trials in which individuals are randomly assigned to one diet or another and followed for many years. Because of practical constraints and cost, few such studies have been conducted, and most of these have focused on patients who already suffer from heart disease. Though limited, these studies have supported the benefits of replacing saturated fat with polyunsaturated fat, but not with carbohydrates. In the most expensive study ever conducted—the Women's Health Initiative—nearly 50,000 women were randomly assigned to either a low-fat diet or their usual diet. The results, reported in early 2006 after approximately eight years, showed no difference in health between the two groups.

The best alternative is to conduct large epidemiological studies in which the diets of many people are periodically assessed and the participants are monitored for the development of heart disease and other conditions. One of the best-known examples of this research is the Nurses' Health Study, which was begun in 1976 to evaluate the effects of oral contraceptives but was soon extended to nutrition as well. Our group at Harvard University has followed nearly 90,000 women in this study who first completed detailed questionnaires on diet in 1980, as well as more than 50,000 men who were enrolled in the Health Professionals Follow-Up Study in 1986.

After adjusting the analysis to account for smoking, physical activity and other recognized risk factors, we found that a participant's risk of heart disease was strongly influenced by the type of dietary fat consumed. Eating trans fat increased the risk substantially, and eating saturated fat increased it slightly. In contrast, eating monounsaturated and polyunsaturated fats decreased the risk—just as the controlled feeding studies predicted. Because these two effects counterbalanced each other, higher overall consumption of fat did not lead to higher rates of coronary heart disease. This finding reinforced a 1989 report by the National Academy of Sci-

Found in many margarines, baked goods and fried foods, trans fats are uniquely bad for you.

THE AUTHORS

WALTER C. WILLETT and *MEIR J. STAMPFER* are professors of epidemiology and nutrition at the Harvard School of Public Health. Willett chairs the school's department of nutrition, and Stampfer heads the department of epidemiology. Willett and Stampfer are also professors of medicine at Harvard Medical School. Both of them practice what they preach by eating well and exercising regularly.

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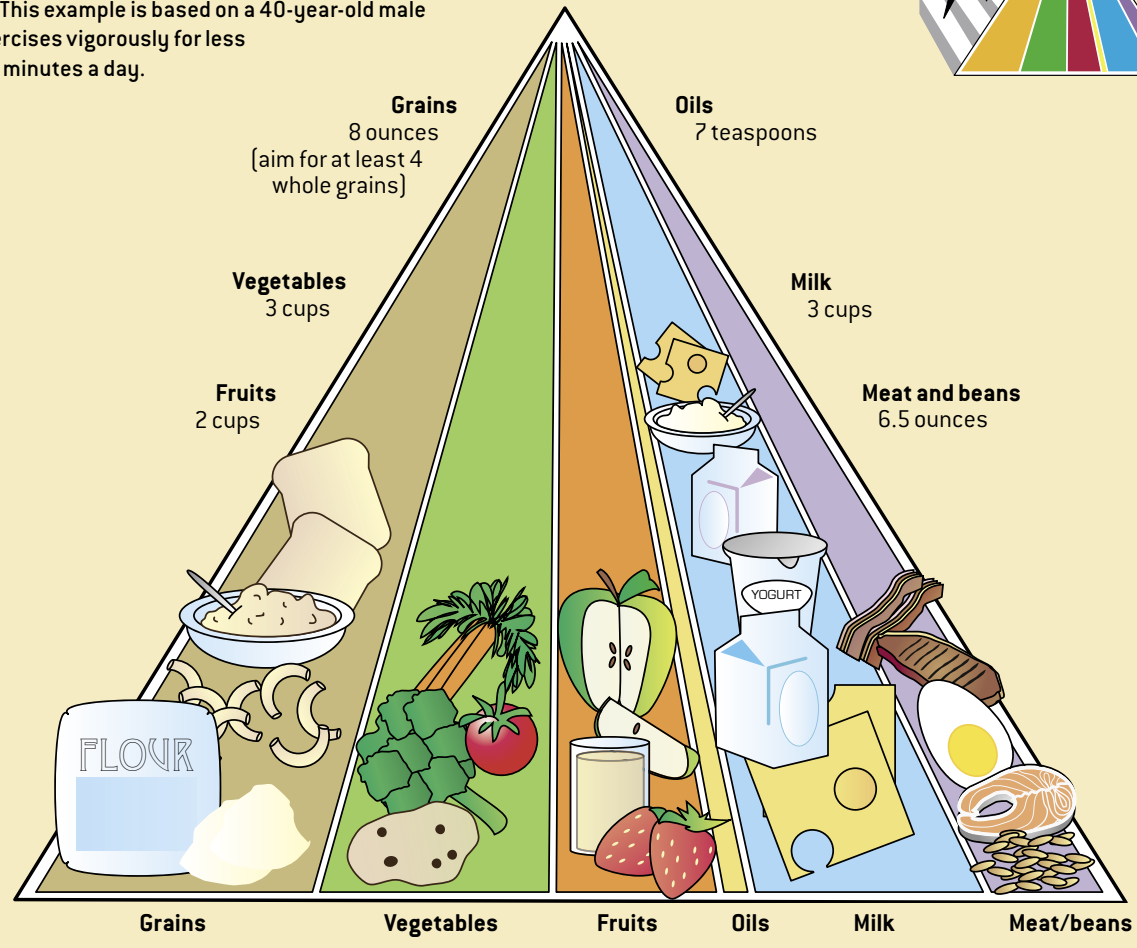
ences that concluded that the type of fat, but not the percentage of calories from total fat, is an important factor in the development of heart disease risk.

But what about illnesses besides coronary heart disease? High rates of breast, colon and prostate cancers in affluent Western countries have led to the belief that the consumption of fat, particularly animal fat, may be a risk factor. But large epidemiological studies have shown little evidence that total fat consumption or intakes of specific types of fat during midlife affect the risks of breast or colon cancer. Some studies have indicated that prostate cancer and the consumption of animal fat may be associated, but reassuringly there is no suggestion that vegetable oils increase any cancer risk. Indeed, some studies have suggested that vegetable oils may slightly reduce such risks.

Finally, one must consider the impact of fat consumption on obesity, the most serious nutritional problem in the U.S. Obesity is a major risk factor for several diseases, including type 2 diabetes (also called adult-onset diabetes), coronary heart disease, and cancers of the breast, colon, kidney and esophagus. Many nutritionists believe that eating fat can contribute to weight gain because fat contains more calories per gram than protein or carbohydrates. Also, the process of storing dietary fat in the body may be more efficient than the conversion of carbohydrates to body fat. But recent controlled feeding studies have shown that these considerations are not practically important. The best way to avoid obesity is to limit your total calories, not just the fat calories. So the critical issue is whether the fat composition of a diet can influence one's ability to control calorie intake. In other words, does eating fat leave you more or less hungry than eating protein or carbohydrates? There are various theories about why one diet should be better than another, but few long-term studies have been done. In randomized trials, individuals assigned to

2005 FOOD PYRAMID

The USDA's newest food pyramid (*below*) emphasizes the importance of exercise (*inset at right*). To get dietary recommendations such as the ones shown here, an individual must visit the Web site www.mypyramid.gov and enter three variables: age, gender and level of daily physical activity. The site then generates a pyramid that is "customized" but does not consider factors such as height and weight. This example is based on a 40-year-old male who exercises vigorously for less than 30 minutes a day.



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low-fat diets tend to lose a few pounds during the first months but then regain the weight. In studies lasting a year or longer, low-fat diets have consistently not led to greater weight loss.

The text accompanying the new pyramid provides some improvement over the 1992 version in recognizing that some fats (trans and saturated) are worse than others (poly and monounsaturated). Unfortunately, it treats trans and saturated fats the same way, even though trans fat from hydrogenated vegetable oils is at least twice as harmful, on a gram-for-gram basis. And unlike saturated fat, it can potentially be eliminated from the diet. Also, the new pyramid largely ignores the positive benefits of healthful oils.

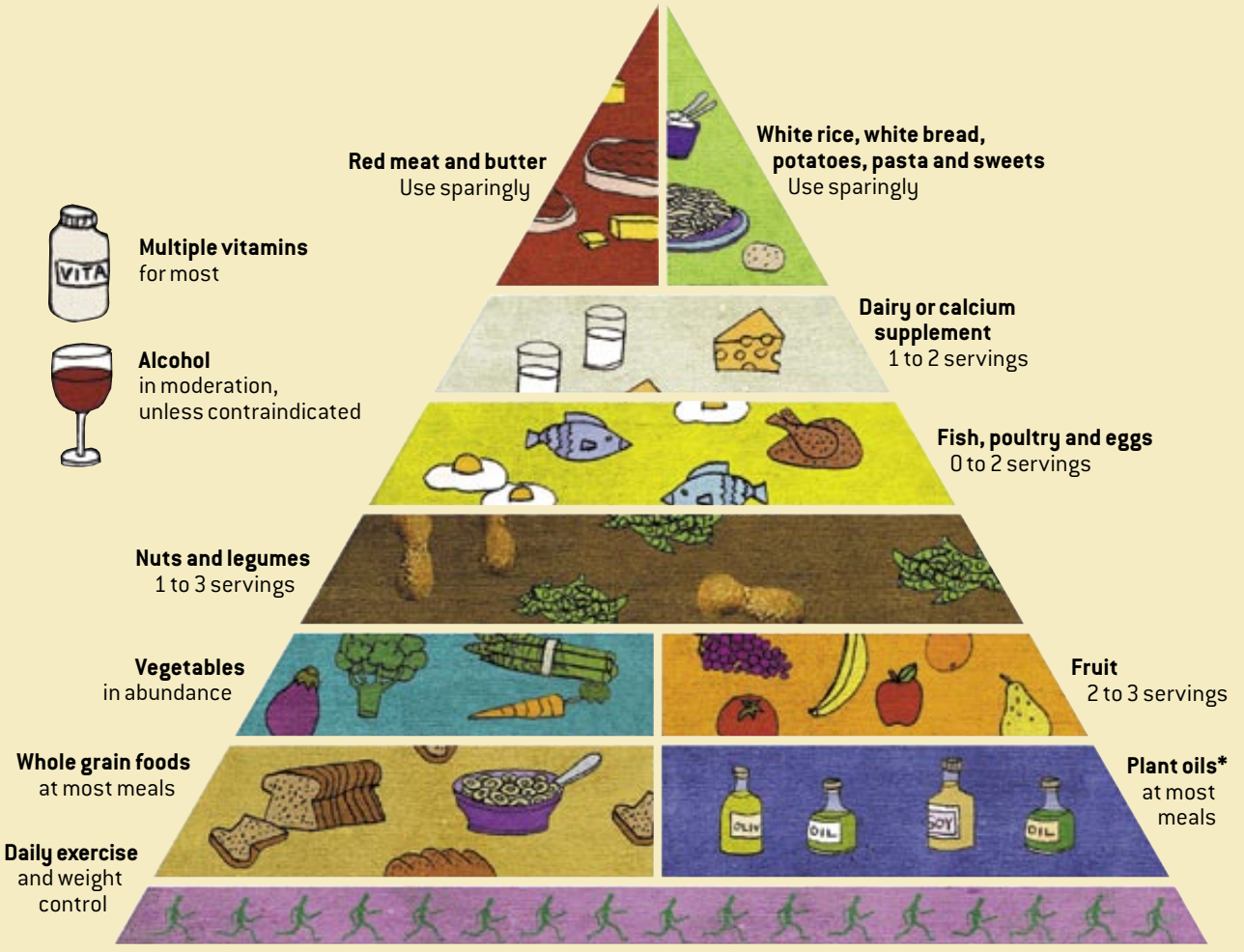
Carbo-Loading

NOW LET'S LOOK at the health effects of carbohydrates. Complex carbohydrates consist of long chains of sugar units such as glucose and fructose; sugars contain only one or two units. Because of concerns that sugars offer nothing but "empty calories"—that is, no vitamins, minerals or other nutrients—complex carbohydrates form the base of the USDA food pyramid. But refined carbohydrates, such as white bread and white rice, can be very quickly broken down to glucose, the primary fuel for the body. The refining process produces an easily absorbed form of starch—which is defined as glucose molecules bound together—and also removes many vitamins and minerals and fiber. Thus, these carbohydrates increase glucose levels in the blood more than whole grains do. (Whole grains have not been milled into fine flour.)

Or consider potatoes. Eating a boiled potato raises blood sugar levels higher than eating the same amount of calories from table sugar. Because potatoes are mostly starch, they can be rapidly metabolized to glucose. In contrast, table sug-

A BETTER FOOD PYRAMID

The authors' proposed pyramid distinguishes between healthy and unhealthy types of fat and carbohydrates. Fruits and vegetables are still recommended, but the consumption of dairy products should be limited.



** Olive, canola, soy, corn, sunflower, peanut and other vegetable oils*

RICHARD BORGE

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ar (sucrose) is a disaccharide consisting of one molecule of glucose and one molecule of fructose. Fructose takes longer to convert to glucose, hence the slower rise in blood glucose levels.

A rapid increase in blood sugar stimulates a large release of insulin, the hormone that directs glucose to the muscles and liver. As a result, blood sugar plummets, sometimes even going below the baseline. High levels of glucose and insulin can have negative effects on cardiovascular health, raising triglycerides and lowering HDL (the good cholesterol). The precipitous decline in glucose can also lead to more hunger after a carbohydrate-rich meal and thus contribute to overeating and obesity.

Eating a boiled potato raises blood sugar levels higher than eating the same amount of calories from table sugar.

In our epidemiological studies, we have found that a high intake of starch from refined grains and potatoes is associated with a high risk of type 2 diabetes and coronary heart disease. Conversely, a greater intake of fiber is related to a lower risk of these illnesses. Interestingly, though, the consumption of fiber did not lower the risk of colon cancer, as had been hypothesized earlier.

Overweight, inactive people can become resistant to insulin's effects and therefore require more of the hormone to regulate their blood sugar. Recent evidence indicates that the adverse metabolic response to carbohydrates is substantially worse among people who already have insulin resistance. This finding may account for the ability of peasant farmers in Asia and elsewhere, who are extremely lean and active, to consume large amounts of refined carbohydrates without experiencing diabetes or heart disease, whereas the same diet in a more sedentary population can have devastating effects.

The new pyramid appropriately provides more emphasis on whole grains, but it still implies that getting half of your grains as refined starch is desirable, whereas these carbohydrate sources should be used sparingly. Further, the new pyramid gives insufficient attention to added sugars and sugar soft drinks, which constitute about 8 percent of all calories consumed in the U.S.—more than any other food item.

Eat Your Veggies

HIGH INTAKE OF FRUITS and vegetables is perhaps the least controversial aspect of the 1992 food pyramid, and the 2005 pyramid gives them even greater emphasis than before. A reduction in cancer risk has been a widely promoted benefit. But most of the evidence for this benefit has come from case-control studies, in which patients with cancer and selected control subjects are asked about their earlier diets. These retrospective studies are susceptible to numerous biases, and recent findings from large prospective studies (including our own) have tended to show little relation between overall fruit and vegetable consumption and cancer incidence. (Specific nutrients in fruits and vegetables may offer benefits, though; for instance, the folic acid in green leafy vegetables may reduce the risk of colon cancer, and the lycopene found in tomatoes may lower the risk of prostate cancer.)

The real value of eating fruits and vegetables may be in reducing the risk of cardiovascular disease. Folic acid and potassium appear to contribute to this effect, which has been seen in several epidemiological studies. Inadequate consumption of folic acid is responsible for higher risks of serious birth defects as well, and low intake of lutein, a pigment in green leafy vegetables, has been associated with greater risks of cataracts and degeneration of the retina. Fruits and vegetables are also the primary source of many vitamins needed for good health. Thus, there are good reasons to consume the recommended five servings a day, even if doing so has little impact on cancer risk. The inclusion of potatoes as a vegetable in the USDA pyramid has little justification, however; being mainly starch, potatoes do not confer the benefits seen for other vegetables.

Another flaw in both the old and new versions of the USDA pyramid is its failure to recognize the important health differences between red meat (beef, pork and lamb) and the other foods in the meat and beans group (poultry, fish, legumes, nuts and eggs). High consumption of red meat has been associated with an increased risk of coronary heart disease, probably because of its high content of saturated fat and cholesterol. Red meat also raises the risk of type 2 diabetes and colon cancer. The elevated risk of colon cancer may be related in part to the carcinogens produced during cooking and the chemicals found in processed meats such as salami and bologna.

Poultry and fish, in contrast, contain less saturated fat and more unsaturated fat than red meat does. Fish is a rich source of the essential omega-3 fatty acids as well. Not surprisingly, studies have shown that people who replace red meat with chicken and fish have a lower risk of coronary heart disease and colon cancer. Eggs are high in cholesterol, but consumption of up to one a day does not appear to have adverse effects on heart disease risk (except among diabetics), probably because the effects of a slightly higher cholesterol level are counterbalanced by other nutritional benefits.

Many people have avoided nuts because of their high fat content, but the fat in nuts, including peanuts, is mainly unsaturated, and walnuts in particular are a good source of omega-3 fatty acids. Controlled feeding studies show that nuts improve blood cholesterol ratios, and epidemiological studies indicate that they lower the risk of heart disease and diabetes. Also, people who eat nuts are actually less likely to be obese; perhaps because nuts are more satisfying to the appetite, eating them seems to have the effect of significantly reducing the intake of other foods.

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Yet another concern regarding both versions of the USDA pyramid is that they promote overconsumption of dairy products, recommending the equivalent of three glasses of milk a day for most individuals. This advice is usually justified by dairy's calcium content, which is believed to prevent osteoporosis and bone fractures. But the highest rates of fractures are found in countries with high dairy consumption, and large prospective studies have not shown a lower risk of fractures among those who eat plenty of dairy products. Calcium is an essential nutrient, but the requirements for bone health have probably been overstated. What is more, we cannot assume that high dairy consumption is safe: in several studies, men who consumed large amounts of dairy products experienced an increased risk of prostate cancer, and in some studies, women with high intakes had elevated rates of ovarian cancer. Although fat was initially assumed to be the responsible factor, this has not been supported in more detailed analyses. High calcium intake itself seemed most clearly related to the risk of prostate cancer.

More research is needed to determine the health effects of dairy products, but at the moment it seems imprudent to recommend high consumption. Most adults who are following a good overall diet can get the necessary amount of calcium by consuming the equivalent of one glass of milk a day. Under certain circumstances, such as after menopause, women may need more calcium, but it can be obtained at lower cost and without saturated fat or calories by taking a supplement.

A Healthier Pyramid

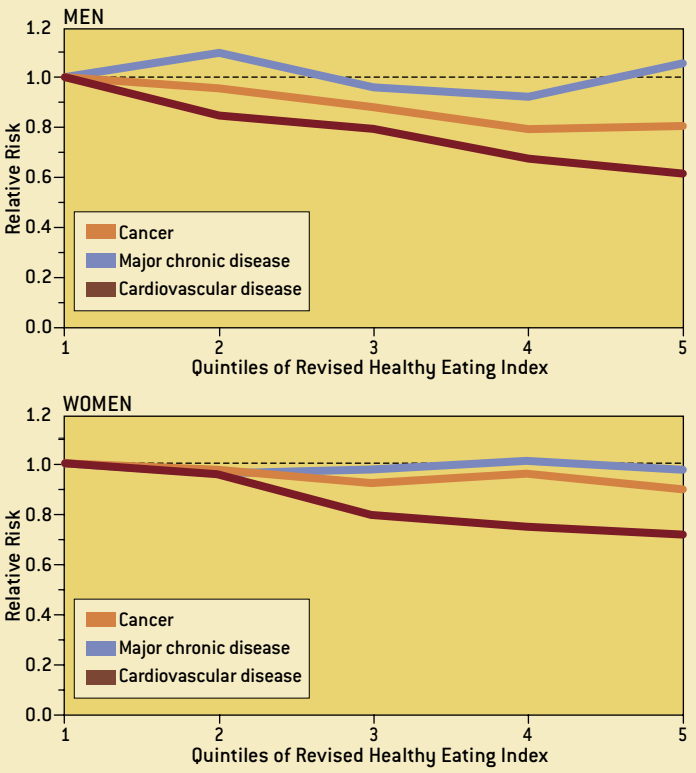
ALTHOUGH THE USDA'S food pyramid has become an icon of nutrition over the past decade, until recently no studies had evaluated the health of individuals who followed its guidelines. It very likely has some benefits, especially from a high intake of fruits and vegetables. And a decrease in total fat intake would tend to reduce the consumption of harmful saturated and trans fats. But the pyramid could also lead people to eat fewer of the healthy unsaturated fats and more starches, so the benefits might be negated by the harm.

To evaluate the overall impact, we used the Healthy Eating Index (HEI), a score developed by the USDA to measure adherence to the 1992 pyramid and its accompanying dietary guidelines in federal nutrition programs. From the data collected in our large epidemiological studies, we calculated each participant's HEI score and then examined the relation of these scores to subsequent risk of major chronic disease (defined as heart attack, stroke, cancer or nontraumatic death from any cause). When we compared people in the same age groups, women and men with the highest HEI scores did have a lower risk of major chronic disease. But these individuals also smoked less, exercised more and had generally healthier lifestyles than the other participants. After adjusting for these variables, we found that participants with the highest HEI scores did not experience significantly better overall health outcomes. As predicted, the 1992 pyramid's harms counterbalanced its benefits. The new pyramid has yet to be evaluated in this manner, but because its basic advice is similar to that given by the earlier pyramid, the effect on health outcomes will probably be similar as well.

The best feature of the new pyramid is its clear emphasis on physical activity. This is laudable but does not help people choose what to eat. The new pyramid provides "customized" dietary advice based on sex and age but regardless of body size—so a six-foot-six-inch-tall, 330-pound man gets the same advice as a 5-foot-3-inch-tall man weighing 120 pounds.

Because the goal of the USDA pyramids was a worthy one—to encourage healthy dietary choices—we have tried to develop an alternative derived from

Benefits of the Proposed Pyramid



HEALTH EFFECTS of the recommendations in the revised food pyramid were gauged by studying disease rates among 67,271 women in the Nurses' Health Study and 38,615 men in the Health Professionals Follow-up Study. Women and men in the fifth quintile (the 20 percent whose diets were closest to the pyramid's recommendations) had significantly lower rates of cardiovascular disease than those in the first quintile (the 20 percent who strayed the most from the pyramid). The dietary recommendations had no significant effect on cancer risk, however.

CORNELIA BLIK

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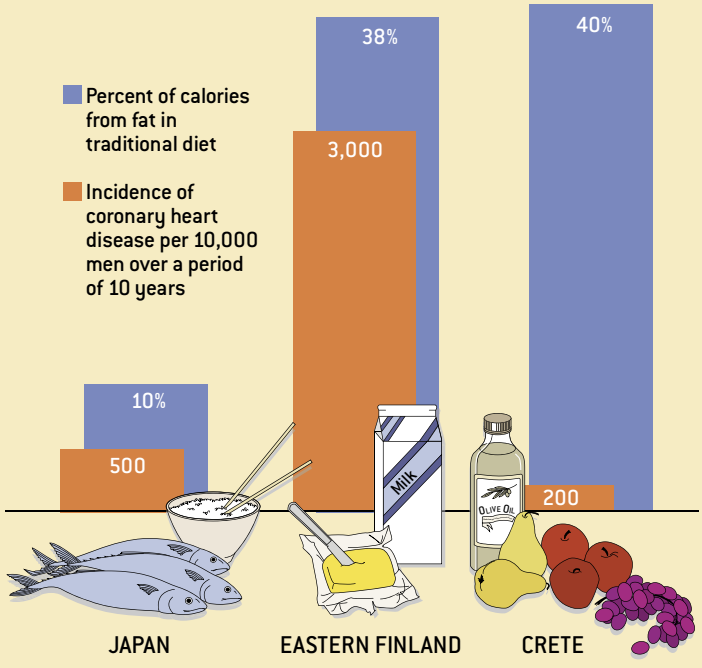
Fat and Heart Disease



INTERNATIONAL COMPARISONS reveal that total fat intake is a poor indicator of heart disease risk. What is important is the type of fat consumed. In regions where saturated fats traditionally made up much of the diet (for example, eastern Finland), rates of heart disease were much higher than in areas where monounsaturated fats were prevalent (such as the Greek island of Crete). Crete's Mediterranean diet, based on olive oil, was even better for the heart than the low-fat traditional diet of Japan.

the best available knowledge. Our revised pyramid [*see box on page 18*] emphasizes weight control through exercising daily and avoiding an excessive total intake of calories. This pyramid recommends that the bulk of one's diet should consist of healthy fats (liquid vegetable oils such as olive, canola, soy, corn, sunflower and peanut) and healthy carbohydrates (whole grain foods such as whole wheat bread, oatmeal and brown rice).

If both the fats and carbohydrates in your diet are healthy, you probably do not have to worry too much about the percentages of total calories coming from each. Fruits and vegetables should also be eaten in abundance. Moderate amounts of healthy sources of protein (nuts, legumes, fish, poultry and eggs) are encouraged, but dairy consumption should be limited to one to two servings a day. The revised pyramid recommends minimizing the consumption of red meat, butter, refined grains (including white bread, white rice and white pasta), potatoes and sugar.

Trans fat does not appear at all in the pyramid, because it has no place in a healthy diet. A multiple vitamin is suggested for most people, and moderate alcohol consumption can be a worthwhile option (if not contraindicated by specific health conditions or medications). This last recommendation comes with a caveat: drinking no alcohol is clearly better than drinking too much. But more and more studies are showing the benefits of moderate alcohol consumption (in any form: wine, beer or spirits) to the cardiovascular system.

Can we show that our pyramid is healthier than the USDA's? We devised a new Healthy Eating Index that measured how closely a person's diet followed our recommendations. Applying this revised index to our epidemiological studies, we found that men and women who were eating in accordance with the new pyramid had a lower risk of major chronic disease [*see box on opposite page*]. This benefit resulted almost entirely from significant reductions in the risk of cardiovascular disease—up to 30 percent for women and 40 percent for men. Following the new pyramid's guidelines did not, however, lower the risk of cancer. Weight control and physical activity, rather than specific food choices, are associated with a reduced risk of many cancers.

Of course, uncertainties still cloud our understanding of the relation between diet and health. More research is needed to examine the role of dairy products, the health effects of specific fruits and vegetables, the risks and benefits of vitamin supplements, and the long-term effects of diet during childhood and early adult life. The interaction of dietary factors with genetic predisposition should also be investigated, although its importance remains to be determined.

Another challenge will be to ensure that the information about nutrition given to the public is based strictly on scientific evidence. The USDA may not be the best government agency to develop objective nutritional guidelines, because it may be too closely linked to the agricultural industry. The food pyramid should be rebuilt in a setting that is well insulated from political and economic interests. SA

MORE TO EXPLORE

Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle. Meir J. Stampfer, Frank B. Hu, JoAnn E. Manson, Eric B. Rimm and Walter C. Willett in *New England Journal of Medicine,* Vol. 343, No. 1, pages 16–22; July 6, 2000.

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Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients). Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academies Press, 2002. Available online at **www.nap.edu/books/0309085373/html/**

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Drink to Your Health?

Three decades of research shows that drinking small to moderate amounts of alcohol has cardiovascular benefits. A thorny issue for physicians is whether to recommend drinking to some patients

Addressing an Illinois temperance society in 1842, Abraham Lincoln said something about "intoxicating liquor" that probably got a frosty reception. "It is true that … many were greatly injured by it," the future president noted. "But none seemed to think the injury arose from the use of a bad thing but from the abuse of a very good thing."

America has always had trouble deciding whether alcohol is a bad thing or a good thing. Millions who remember Prohibition, when all alcoholic beverages were illegal, now witness a constant stream of advertisements from producers of alcoholic beverages encouraging people to drink. Despite alcohol's popularity today, however, many still consider abstinence a virtue. Certainly heavy drinking and alcoholism deserve deep concern for the terrible toll they take on alcohol abusers and society in general. But worry about the dangers of abuse often leads to emotional denials that alcohol could have any medical benefits. Such denials ignore a growing body of evidence indicating that moderate alcohol intake wards off certain cardiovascular (circulatory system) conditions, most notably heart attacks and ischemic strokes (those caused by blocked blood vessels). A few studies even show protection against dementia, which can be related to cardiovascular problems.

By **Arthur L. Klatsky**

Photographs by Tina West

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The large arteries of people who died of alcoholic liver cirrhosis were remarkably free of atherosclerosis.

The Alcohol Effect

A DISCUSSION OF moderate drinking requires a working definition of "moderate." Simple definitions of light, moderate or heavy are somewhat arbitrary, but a consensus in the medical literature puts the upper limit for moderate drinking at two standard-size drinks a day [*see box on opposite page*]. Studies show that drinking above that level can be harmful to overall health, although sex, age and other factors lower and raise the boundary for individuals.

The main medical benefit of reasonable alcohol use seems to be a lowering of the risk for coronary heart disease (CHD), which results from the buildup of atherosclerosis (fatty plaque) in the arteries that bring blood to the heart.

Atherosclerosis restricts blood flow to the heart and can promote the formation of vessel-blocking clots. It can thereby cause angina (chest discomfort resulting from low oxygen levels in the heart muscles), heart attack (the death of heart tissue that occurs when a blood clot or narrowing of the arteries prevents blood from reaching the heart) and death, often without warning. The condition usually starts at a young age but takes decades to blossom into overt CHD. The most common form of heart disease in developed countries, CHD causes about 60 percent of deaths from cardiovascular ills and about 25 percent of *all* deaths in those nations.

Pathologists uncovered the first clues to the value of alcohol in the early 1900s, noting that the large arteries of people who died of alcoholic liver cirrhosis seemed remarkably "clean"—that is, free of atherosclerosis. One explanatory hypothesis assumed that alcohol was a nebulous solvent, essentially dissolving the buildup in the arteries; another explanation held that heavier drinkers died before their atherosclerosis had a chance to develop. Neither idea truly explained drinkers' unblocked arteries, however.

A more telling hint emerged in the late 1960s, when Gary D. Friedman of the Kaiser Permanente Medical Center in Oakland, Calif., came up with a novel idea: use computers to unearth unknown predictors of heart attacks. The power of computing could first identify healthy people who had risk factors similar to heart attack victims. Such factors include cigarette smoking, high blood pressure, diabetes, elevated levels of low-density-lipoprotein (LDL, or "bad") cholesterol, low levels of high-density-lipoprotein (HDL, or "good") cholesterol, male gender, and a family history of CHD. Friedman then searched for predictors of heart attacks by comparing the patients and the newly found controls in hundreds of ways—for example, their exercise and dietary habits and their respective levels of various blood compounds. The computers spit out a surprising discovery: abstinence from alcohol was associated with a higher risk of heart attack.

Various studies had missed the connection because they neglected to examine alcohol use as a behavior separate from smoking. We now know that because drinkers often also use cigarettes, the negative impact of smoking was masking the beneficial effect of alcohol. In 1974 my Kaiser Permanente colleagues Friedman and Abraham B. Siegelaub and I were the first, to our knowledge, to publish an examination of moderate drinking in the absence of smoking. We saw a clear connection between alcohol consumption and a decreased risk of heart attack.

Since then, dozens of investigations in men and women of several racial groups in various countries have correlated previous alcohol use with current health. These studies have firmly established that nondrinkers develop both fatal and nonfatal CHD more often than do light to moderate drinkers. In 2000 Giovanni Corrao of the University of Milan-Bicocca in Italy, Kari Poikolainen of the Järvenpää Addiction Hospital in Finland and their colleagues combined the results of 28 previously published investigations on the relation between alcohol intake and CHD. In this meta-analysis, they found that the risk of developing CHD went down as the amount of alcohol consumed daily went up from zero to 25 grams. At 25 grams—the amount of alcohol in about two standard drinks—an individual's risk of a major CHD event, either heart attack or death, was 20 percent lower than for someone who did not drink at all.

Recent data about alcohol protecting against death from CHD are even more impressive. At a meeting of the American Heart Association in November 2002 my Kaiser Permanente colleagues Friedman, Mary Anne Arm-

OVERVIEW
ALCOHOL & HEART HEALTH

- An assortment of studies from around the world indicates that drinking in small to moderate amounts decreases the risk of dying from coronary heart disease (CHD) by almost one third.
- Some research points to red wine as being particularly protective against coronary heart disease. Other healthful habits of red wine drinkers, however, may be partly responsible for the apparent effect.
- A select group of people—those with CHD or at risk for CHD and without risks associated with alcohol itself—may wish to consult their physicians about moderate drinking as part of a heart-healthy diet.

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"Standard" Servings of Alcoholic Beverages

NO FORMAL DEFINITION of a standard-size drink exists, although something of a consensus does. Beer is often sold in a 12-ounce bottle or can, which is a useful reference point as one standard drink. The amount of alcohol, about 0.6 ounce, in 12 ounces of beer is virtually the same as is found in a five-ounce glass of wine or a 1.5-ounce glass of distilled spirits, such as vodka, gin, bourbon or scotch. Wine and distilled spirits in these amounts are thus also considered standard drinks.

strong and Harald Kipp and I discussed an updated analysis of 128,934 patients who had checkups between 1978 and 1985, with 16,539 of them dying between 1978 and 1998. CHD was responsible for 3,001 of those deaths. We discovered that those who had one or two alcoholic drinks a day had a 32 percent lower risk of dying from CHD than abstainers did.

The possible mechanisms by which alcohol has such an apparently profound effect on cardiovascular health primarily involve cholesterol levels and blood clotting. Blood lipids, or fats, play a central role in CHD. Numerous studies show that moderate drinkers have 10 to 20 percent higher levels of heart-protecting HDL cholesterol. And people with higher HDL levels, also known to be increased by exercise and some medications, have a lower risk of CHD.

That lower risk stems from HDL's ability to usher LDL cholesterol back to the liver for recycling or elimination, among other effects. Less cholesterol then builds up in the walls of blood vessels, and so less atherosclerotic plaque forms. Alcohol has a greater influence on a different HDL subspecies (HDL_3) than on the type increased by exercise (HDL_2), although both types are protective. (The biochemical pathways in the liver that could account for alcohol's ability to raise HDL levels remain incompletely known; it is thought that alcohol affects liver enzymes involved in the production of HDL.) Three separate analyses aimed at determining specific contributions of alcohol all suggest that the higher HDL levels of drinkers are responsible for about half of the lowered CHD risk.

Alcohol may also disrupt the complex biochemical cascade behind blood clotting, which can cause heart attacks when it occurs inappropriately, such as over atherosclerotic regions in coronary arteries. Blood platelets, cellular components of clots, may become less "sticky" in the presence of alcohol and therefore less prone to clumping, although data on this question remain ambiguous. A 1984 study by Raffaele Landolfi and Manfred Steiner of Brown University's Memorial Hospital revealed that alcohol intake increases the level of prostacyclin, which interferes with clotting, relative to the level of thromboxane, which promotes clotting. Walter E. Laug of the University of Southern California Keck School of Medicine showed that alcohol raises levels of plasminogen activator, a clot-dissolving enzyme. Finally, several studies suggest that alcohol lowers levels of another promoter of blood clots, fibrinogen.

Overall, alcohol's anticlotting capacity is not as well established as its HDL effect, and some effects, such as platelet clumping, may be reversed by heavy or binge drinking. Nevertheless, anticlotting appears to have a role in the lower risk for heart attacks enjoyed by moderate drinkers. In addition, studies have shown a beneficial effect on CHD risk in people who have far fewer than two drinks a day—say, three or four drinks a week. Anticlotting could be a major factor in the protection accorded by alcohol in these small amounts, which seem insufficient to affect HDL levels greatly.

Although alcohol reduces heart disease risk mainly by raising HDL levels and reducing clotting, it probably acts in other ways as well. Moderate drinking may lessen CHD risk indirectly by decreasing the risk of type 2 (adult-onset) diabetes, which is a powerful predictor of CHD. This benefit appears to

THE AUTHOR

ARTHUR L. KLATSKY is a senior consultant in cardiology and an adjunct investigator at the division of research at the Kaiser Permanente Medical Center in Oakland, Calif. A graduate of Harvard Medical School, he headed the medical center's division of cardiology from 1978 to 1994 and directed its coronary care unit from 1968 to 1990. Since 1977 he has been principal investigator of a series of studies of the link between drinking alcoholic beverages and health. His 1974 *Annals of Internal Medicine* article [see More to Explore, on page 29] was the first published epidemiological report of an inverse relation between alcohol drinking and coronary disease; it was cited in 1995 by the National Institute on Alcohol Abuse and Alcoholism as one of 16 seminal articles in alcohol research. His most recent honor was the Morris Collen Lifetime Achievement Research Award by Kaiser Permanente in 2004. Klatsky has completed six marathons and in 1990 climbed Mount Kilimanjaro.

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Drinking: Risks & Benefits

LIGHT/MODERATE DRINKING

RISKS

Established
Heavy drinking

Unresolved
Breast cancer
Fetal damage

Unlikely
Bowel cancer
Hemorrhagic stroke
High blood pressure

BENEFITS

Probable
Decreased risk of CHD
Decreased risk of ischemic stroke
Decreased risk of gallstones

Possible
Decreased risk of diabetes
Decreased risk of peripheral vascular disease (narrowing or clogging of the arteries carrying blood to the arms and legs)

HEAVY DRINKING

RISKS

Noncardiovascular
Liver cirrhosis
Pancreatitis
Certain cancers
Accidents
Homicides
Suicides
Fetal damage
Degenerative disorders of the central nervous system

Cardiovascular
High blood pressure
Arrhythmia
Hemorrhagic stroke
Cardiomyopathy (damaged heart muscle)

BENEFITS

None

be related to enhanced insulin sensitivity, which promotes proper glucose usage. (Heavy drinking, however, has been connected to higher blood glucose levels, a marker for future diabetes.) Evidence is also growing that inflammation contributes to CHD, and alcohol's anti-CHD power may be related to an anti-inflammatory action on the endothelial tissue that lines blood vessels.

Before accepting alcohol's benefits, an epidemiologist attempts to locate hidden factors possibly at work. For instance, could lifelong abstainers differ from drinkers in psychological traits, dietary habits, physical exercise habits or other ways that might account for their higher CHD risk without the need to invoke the absence of alcohol? Were such traits to explain away alcohol's apparent protection, they would need to be present in both sexes, various countries and several racial groups. Considering that no such traits have been identified, the simpler and more plausible explanation is that light to moderate alcohol drinking does indeed enhance cardiovascular health.

In fact, the available evidence satisfies most standard epidemiological criteria for establishing a causal relation. The numerous studies examining light and moderate alcohol intake and health reach consistent conclusions. The prospective studies that exist have the correct temporal sequence—that is, individuals' habits of interest are identified, after which their health is monitored over the long term, and alcohol users have different health profiles than nondrinkers do. The positives associated with alcohol can be attributed to biologically plausible mechanisms. Alcohol offers specific enhancement of cardiovascular health, not general protection against all illness. And alcohol's effect can be identified independent of known "confounders," other alcohol-related factors that could be responsible for a subject's cardiovascular condition.

The 30 percent reduction in risk is, perhaps surprisingly to some, less convincing evidence than the arguments above, because a strong *unknown* confounder could still account for the connection. To take an extreme example, consider a hypothetical set of genes that confers on the possessor 60 percent less CHD risk and causes a strong predisposition toward liking moderate amounts of alcohol. The independent consequences of the genes could appear causally linked. In fact, however, no such confounder is known or likely.

Because heavy drinking is not more protective than lighter drinking, this absence of a clear dose-response relation is also a weakness. Nevertheless, the collected data make a strong case for the cardiac benefits of controlled drinking. I should note, however, that the kind of study considered to be the gold standard in human research—a prospective randomized blinded clinical trial—has not yet been done. Such a study might, for example, engage a large pool of nondrinkers, half of whom, chosen at random and without the knowledge of the researchers, would commence a moderate drinking regimen, while the other half remained abstainers. The two groups would be followed for years in a search for eventual differences in cardiovascular disease and heart-related deaths.

To Drink or Not to Drink

MOST PEOPLE DRINK for reasons other than alcohol's health benefits, and many of them are already using alcohol in amounts that appear to promote cardiovascular health. But the accumulated research on alcohol's positive effects presents a challenge to physicians. On one hand, mild to moderate drinking seems better for heart health than abstinence for select people. On the other hand, heavy drinking is clearly dangerous. It can contribute to noncardiovascular conditions such as liver cirrhosis, pancreatitis, certain cancers and degenerative neurological disorders, and it plays a part in great numbers of accidents, homicides and suicides, as well as in fetal alcohol syndrome. (No conclusive evidence links light to moderate drinking to any of these problems, but underreporting of drinking amount by some heavy drinkers clouds the issue for several conditions.)

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Heavy drinking also contributes to cardiovascular disorders. Too much alcohol raises the risk of alcoholic cardiomyopathy, in which the heart muscle becomes too weak to pump efficiently; high blood pressure (itself a risk factor for CHD, stroke, heart failure and kidney failure); and hemorrhagic stroke, in which blood vessels rupture in or on the surface of the brain. Alcohol overindulgence is also related to "holiday heart syndrome," an electrical signal disturbance that disrupts the heart rhythm. The name refers to its increased frequency around particular holidays during which people engage in binge drinking.

Heart failure is a common consequence of various cardiovascular diseases. Usually defined as the inability of the heart to meet the blood supply needs of the body, heart failure is associated with CHD about 60 percent of the time and with other conditions (such as high blood pressure, heart valve disease, and other heart muscle diseases) in the other 40 percent. A recent report from our group showed that heart failure associated with CHD was substantially less likely in alcohol drinkers of any amount, whereas heart failure associated with other cardiac problems was unrelated to moderate drinking but more likely to occur in heavy alcohol drinkers.

Given the potential dangers of alcohol, how can individuals and their physicians make the decision as to whether to include alcoholic beverages in their lives and, if so, in what amounts? The ability to predict accurately an individual's risk of a drinking problem would be a great boon; the least disputed possible consequence of moderate drinking is problem drinking. Individual risk can be approximated using family and personal histories of alcohol-related problems or conditions, such as liver disease or, of course, alcoholism. Even

Wine, Beer or Spirits?

Beer, wine and liquor all seem to be related to a lower risk of coronary heart disease. A tantalizing question, however, is whether one kind of drink—wine, for example—is better than the others. The short answer: the jury is still out.

The death rate from CHD in France, where red wine consumption is common, is only about half that in the U.S., despite similar fat intake and sedentary lifestyles. That observation led to the catchphrase "the French paradox" and the idea that red wine is *the* beneficial alcoholic beverage. This belief has a hypothetical basis—red wine especially contains a number of ingredients with potential antioxidant and other atherosclerosis-fighting benefits.

An excellent 1995 Danish study, in which almost 13,000 people were followed during a 12-year period, suggested that wine drinkers have lower death rates from CHD than do other alcohol imbibers. My Kaiser Permanente colleagues Mary Anne Armstrong and Gary D. Friedman and I published on the risk of CHD death (in 1990) and the risk of CHD hospitalization (in 1997); in these investigations, which included almost 130,000 Californians, wine and beer drinkers had a lower CHD risk than did hard-liquor drinkers. At a meeting of the American Heart Association in November 2002, I presented new data that updated the 1990 study. We were surprised to find that those drinking wine daily had about a 25 percent lower risk of CHD death than did those who drank beer and wound up taking in the same amount of alcohol. And the wine drinkers had about a 35 percent lessened CHD death risk compared with the light to moderate hard-liquor drinkers. Significantly, there was no difference in apparent benefit between red wine and white wine.

A vexing complication of all these studies, however, is that the overall habits of wine drinkers, beer drinkers and hard-liquor drinkers tend to differ greatly. In Denmark, for example, wine drinking goes hand in hand with a healthful diet (high in fruits, vegetables, fish, salads and olive oil) and two other markers for better health in general: higher socioeconomic status and higher IQ. In our California studies, those who preferred wine also smoked less, had more education and had more temperate drinking habits than those who preferred beer or hard liquor.

Lifestyle differences among those who prefer one type of alcoholic beverage over another thus make it exceedingly difficult to determine whether the differences in apparent health effects are actually related to the beverage type itself (and therefore to wine constituents besides alcohol), to drinking pattern (imbibed slowly and with food, and on more days per week, for wine) or to other factors. —*A.L.K.*

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The collected data make a strong case for the cardiac benefits of controlled drinking.

when known factors are taken into account, however, unpredictable events late in life may result in deleterious drinking changes.

Exactly because of these dangers, public health concerns about alcohol until recently have been appropriately focused solely on the reduction of the terrible social and medical consequences of heavy drinking. And the correlation between total alcohol consumption in society and alcohol-related problems has been used to justify pushes for abstinence. Ultimately, however, a more complex message is necessary. Merely recommending abstinence is inappropriate health advice to people such as established light drinkers at high risk of

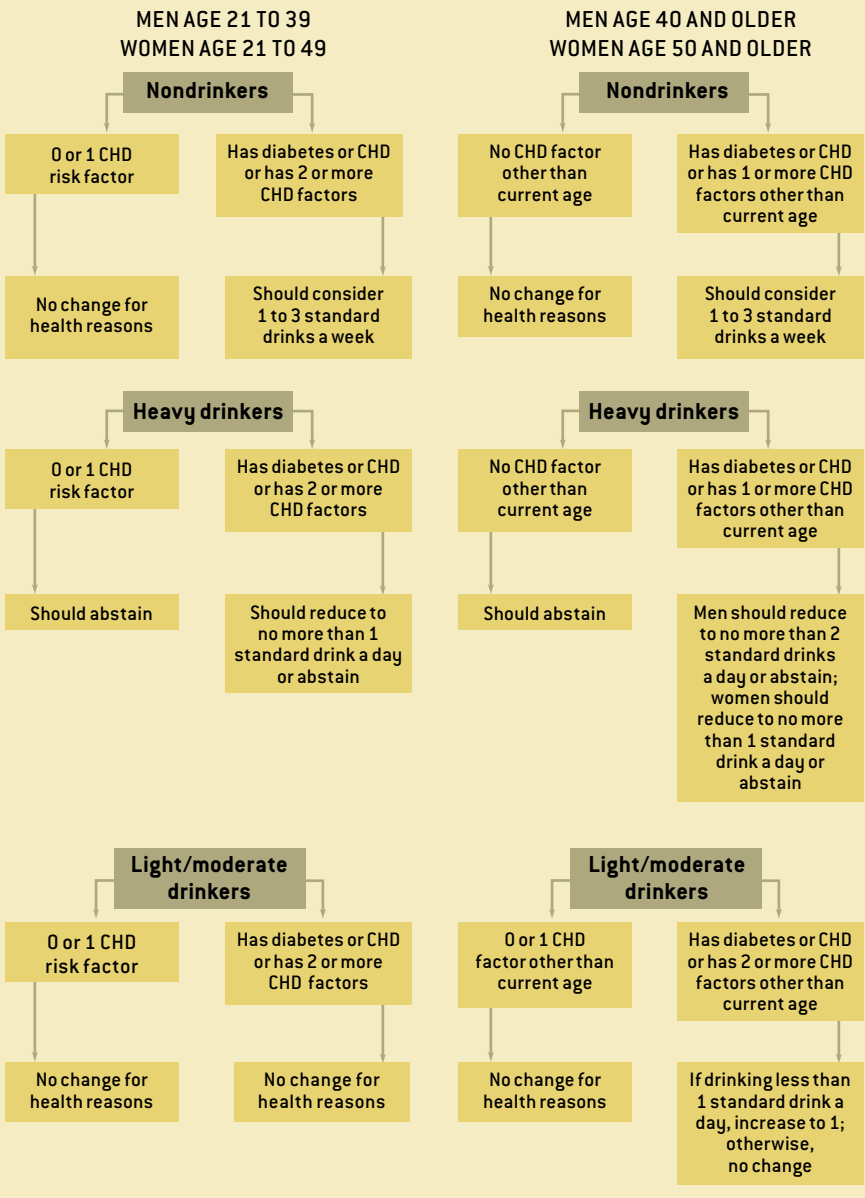
MAKING THE DRINKING DECISION

Roger R. Ecker, a cardiovascular surgeon until recently at the Alta Bates Summit Medical Center in Oakland, Calif., and I developed these charts to help individuals determine whether to include alcoholic beverages, and in what amounts, in their diets. The charts are designed to be used by physicians in consultation with patients. Coronary heart disease risk factors are listed at the bottom. "Light/moderate" is defined as up to one standard drink a day for women and up to two standard drinks a day for men. "Heavy" is three or more drinks a day for men and two or more drinks a day for women.

These charts do *not* apply to the following people, who should abstain from alcohol: anyone under age 21; pregnant women; nondrinkers with a family history of alcoholism, with moral or religious beliefs that preclude alcohol, with a personal history of alcohol abuse, with known organ damage from alcohol, with any chronic liver disease, or with a genetic risk of breast or ovarian cancer. —*A.L.K.*

CHD risk factors, according to National Cholesterol Education Program guidelines:

1. *Family history of CHD (father or brother younger than 55 with CHD, mother or sister younger than 65 with CHD)*
2. *Smoking*
3. *High blood pressure*
4. *Total cholesterol higher than 200*
5. *HDL cholesterol lower than 35 (if HDL is higher than 60, subtract one risk factor)*
6. *Age 40 and older for men, 50 and older for women*


MEN AGE 21 TO 39
WOMEN AGE 21 TO 49
Nondrinkers
0 or 1 CHD risk factor
Has diabetes or CHD or has 2 or more CHD factors
No change for health reasons
Should consider 1 to 3 standard drinks a week
Heavy drinkers
0 or 1 CHD risk factor
Has diabetes or CHD or has 2 or more CHD factors
Should abstain
Should reduce to no more than 1 standard drink a day or abstain
Light/moderate drinkers
0 or 1 CHD risk factor
Has diabetes or CHD or has 2 or more CHD factors
No change for health reasons
No change for health reasons
MEN AGE 40 AND OLDER
WOMEN AGE 50 AND OLDER
Nondrinkers
No CHD factor other than current age
Has diabetes or CHD or has 1 or more CHD factors other than current age
No change for health reasons
Should consider 1 to 3 standard drinks a week
Heavy drinkers
No CHD factor other than current age
Has diabetes or CHD or has 1 or more CHD factors other than current age
Should abstain
Men should reduce to no more than 2 standard drinks a day or abstain; women should reduce to no more than 1 standard drink a day or abstain
Light/moderate drinkers
0 or 1 CHD factor other than current age
Has diabetes or CHD or has 2 or more CHD factors other than current age
No change for health reasons
If drinking less than 1 standard drink a day, increase to 1; otherwise, no change

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How Alcohol Might Protect against CHD

ALCOHOL EFFECT	PROBABLE ACTION	EVIDENCE
Raises blood HDL cholesterol	Removes and transports LDL cholesterol from vessel wall	Solid supporting evidence; effect explains at least half of alcohol's benefit
Lowers blood LDL cholesterol	Reduces level of one major CHD risk factor	Evidence weak; effect probably not independent of diet
Lowers the oxidation of LDL	Prevents the plaque formation associated with LDL oxidation	Largely hypothetical, although antioxidants are plentiful in red wine
Lowers levels of fibrinogen in blood	Lessens the risk of clot formation on atherosclerotic plaques	Moderate supporting data
Exerts other anticlotting actions: lessens platelet stickiness; raises levels of prostacyclin; lowers levels of thromboxane	Lessens the risk of clot formation on atherosclerotic plaques	Inconsistent data; possible reversal of effect with heavy or binge drinking
Lessens insulin resistance	Lessens key risk factor for adult-onset diabetes and atherosclerosis	Evidence comes from a moderate number of studies
Lessens psychosocial stress	Unclear	No supporting data or likely mechanism
Improves conditioning of heart muscle	Imparts better resistance to damage from oxygen deprivation	Preliminary supporting evidence

CHD and at low risk of alcohol-related problems—which describes a large proportion of the population. Of course, the most important steps for this group are proper diet and exercise; effective treatment of obesity, diabetes, high blood pressure and high cholesterol; and avoidance of tobacco. But there is a place on that list of beneficial activities for light drinking. Most light to moderate drinkers are already imbibing the optimal amount of alcohol for cardiovascular benefit, and they should continue doing what they are doing.

Abstainers should never be indiscriminately advised to drink for health; most have excellent reasons for not drinking. Yet there are exceptions. One case is the person with CHD who "goes clean"—quits smoking, switches to a spartan diet, starts exercising and, with good intentions, gives up the habit of a nightly bottle of beer or glass of wine. This self-imposed prohibition should be repealed. In addition, a number of infrequent drinkers might think about increasing their alcohol intake to one standard drink daily, especially men older than 40 and women older than 50 at high risk of CHD and low risk of alcohol-related problems. But women also have to consider one possible drawback of alcohol: several studies link heavy drinking—and a few even link light drinking—to an increased risk of breast cancer, a less common condition than heart disease in postmenopausal women but certainly quite a serious one. For young women, who are generally at low short-term risk of CHD and therefore may not benefit greatly from alcohol's positive cardiovascular effects, this possible breast cancer link looms larger in estimating the overall risks and benefits of alcohol. Many public health officials recommend that women limit their intake to one drink a day.

The only clear-cut message regarding alcohol and health, then, is that all heavy drinkers should reduce or abstain, as should anyone with a special risk related to alcohol, such as a family or personal history of alcoholism or preexisting liver disease. Beyond that, however, the potential risks and benefits of alcohol are best evaluated on a case-by-case basis. Cardiovascular surgeon Roger R. Ecker and I constructed an algorithm that can help health practitioners and their patients decide how much—if any—alcohol is right for a given individual [*see box on opposite page*].

In short, health professionals should provide balanced, objective guidelines regarding their patients' use of alcohol, and such advice needs to be tailored to each person. I believe that it is possible to define a clear, safe limit for alcohol consumption that would offer a probable benefit to a select segment of the population. The ancient Greeks urged "moderation in all things." Three decades of research shows that this adage is particularly appropriate when it comes to alcohol. SA

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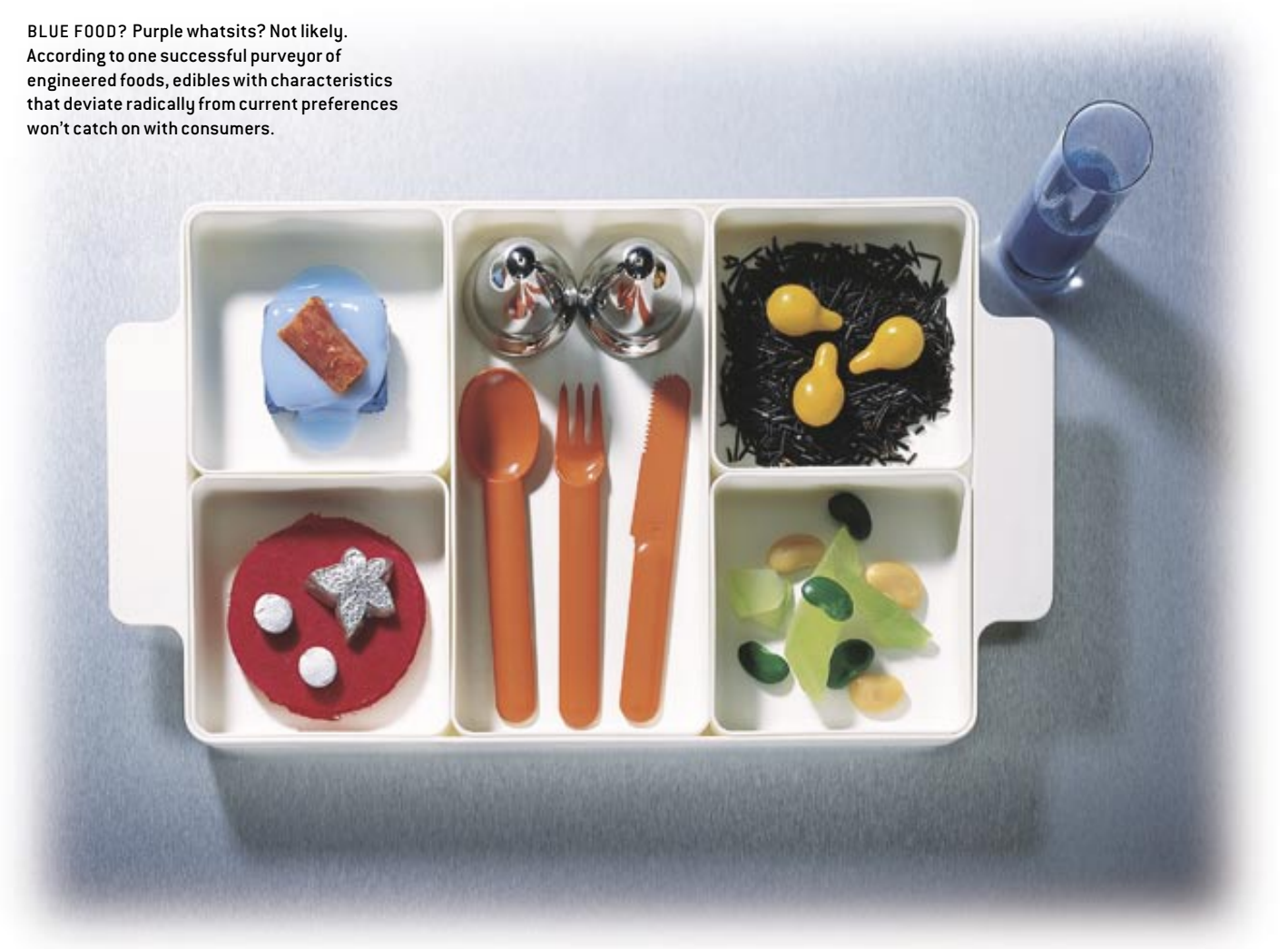

BLUE FOOD? Purple whatsits? Not likely. According to one successful purveyor of engineered foods, edibles with characteristics that deviate radically from current preferences won't catch on with consumers.

DAN WAGNER

Future Feast

Even the meat and potatoes are being reinvented: the meat could come from a test tube, and the potatoes could ward off cholera

By **Jim Kling**

You ease open the refrigerator door to take stock after returning to town from your summer home. The situation isn't so grim after all: there's that romaine lettuce you bought six months ago, still looking fresh and crisp. A chunk of Parmesan, picked up—what year is this again? And down on the bottom shelf: vegetables of various vintages and, there it is, that nice piece of cooked, shrink-wrapped synthetic chicken. It has been in your refrigerator longer than some of your neckties have been in your closet. Just as you realize that the scratchiness in the back of your throat is not going away, you come across a little bottle of antiviral salad dressing. That clinches it. Chicken Caesar salad it is.

Although that scenario may sound a little strange, tomorrow's world of high-tech foods would most likely seem as fantastic to us as microwaves, frozen meals and today's wide selection of produce would have appeared to a cook just 50

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years ago, let alone 100. Many of the details of how food will taste and look, and how it will be packaged and prepared, will depend on those most elusive of intangibles, consumer tastes and preferences. Nevertheless, several trends seem to be gathering momentum, offering glimpses of what and how we might be eating early in the next century.

One is the explosive growth lately in sales of dietary supplements and the advent of so-called functional foods, which contain additives that confer physiological benefits beyond simple nutrition. In addition, tasty new forms of protein—including steaks and fillets grown in chambers rather than as part of an animal—as well as packaging that lets produce breathe and treatments that kill harmful bacteria with radiation or pressure are all likely to be a part of the 21st-century dinner table.

Supercharged Food

ONE OF THE MOST REMARKABLE phenomena in nutrition in recent years is the rise of dietary supplements and, in particular, of "sports supplements" aimed at weight lifters and other physically active people. In 2005 Americans spent more than $21 billion on dietary supplements, according to Grant Ferrier, editor of the *Nutrition Business Journal* in San Diego. About $2.2 billion of that total was spent on sports nutrition.

Such supplements could be just the first entries in a burgeoning market for supercharged food. "Most of the sports supplements are designed to produce benefits centered on control of body composition and energy," says A. Scott Connelly, founder of Met-Rx Engineered Nutrition, now headquartered in Bohemia, N.Y. "People are realizing that the simple calorie theory of body fat control is hopelessly inadequate. For example, supplementing regular dietary intake with lean protein assists the body in burning fat," he maintains.

Connelly further notes that many staple foods such as rice and potatoes are poor sources of vitamins, minerals and other nutrients. Although nutritional supplement companies have long recognized this problem and marketed daily multivitamins and minerals to meet it, "I can tell you as a doctor that human beings don't like to take pills," he insists. "Probably less than 25 percent of people with high blood pressure comply with their prescription. Increasing nutrient density [of traditional foods] has to be a primary goal."

As an example, Connelly cites pizza, "the nutritional Antichrist." Met-Rx's nutritionists have experimented with the humble pizza, the quintessential food for the masses. Met-Rx's reengineered nine-inch pie has only 650 calories. Moreover, the enhanced slice contains 75 grams of a high-quality protein—about four times more than usual. It also has 160 percent of the recommended daily allowance of calcium and 300 percent more lycopene. This plant pigment, which gives the tomato its red color, is also an antioxidant that has been linked in some studies to reduced incidence of heart disease and prostate cancer.

Where might it all lead? If you are waiting for a nutrient-packed food pill, a favorite of 1950s science fiction, you will be disappointed. According to Connelly, food will have to be "in sync with current taste and texture preferences. We won't be successful in trying to get people to abandon their tastes for sweets and fats."

Immunity-Boosting Produce

ANOTHER PIECE OF EVIDENCE that the age of high-tech foods had begun was the 1999 introduction of the margarine Benecol. Clinical trials show that eaten regularly in sufficient quantities, the product's plant stanol esters can reduce the risk of heart disease by lowering levels of potentially harmful, low-density lipoproteins. The margarine is an example of a functional food or "nutraceutical," whose additives provide one or more specific health benefits beyond simple nutrition.

Such foodstuffs could be the basis of an industry raking in $34 billion by the year 2020, Ferrier predicts. Indeed, they are already carving out a sizable niche in Japan, he adds. Cutting cholesterol would only be the beginning; experts foresee products that would do anything from boosting your immune system to fighting seasonal allergies. For the seriously overweight, for example, there could be foods containing dietary hormones such as glucagon, which causes some people to feel full after eating modestly.

Suppose your doctor tells you, 15 years from now, that you have a mild form of diabetes. Rather than closely monitoring your food intake and blood sugar levels, as you would probably have to do today, you might be able to find everything you need to stay healthy in your local supermarket's health food section. No, not the dreaded row lined with organic granola and sprouts but rather an aisle with foods containing additives that, to continue our example, regulate insulin activity and keep your blood sugar under control.

According to John P. Troup, now at Novartis Nutrition Corporation in St. Louis, to produce an effective functional food scientists must "identify the mechanism in the body that is causing some response." That means identifying the individual proteins that carry out the process and then designing a molecule to enhance or discourage the response. Once made, such molecules could be used as food additives.

These foods won't be limited to a prescription aisle. Many common fruits or vegetables could be genetically engineered to produce vaccines for common childhood diseases. In fact, researchers at the Loma Linda University School of Medicine have already genetically engineered potatoes to produce trace amounts of a cholera toxin that could immunize the diner, helping his or her system to resist cholera bacteria.

"More and more, the supermarket is going to become a health care provider store, rather than just a place you buy

THE AUTHOR

JIM KLING is a freelance science and technology writer in Bellingham, Wash. He writes frequently about biotechnology and drug discovery. Much of his focus is on how economic, regulatory and political forces influence the biotechnology industry. He also tries his hand at science fiction from time to time. Kling has mixed feelings about the idea of a synthetic fish fillet sandwich.

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your food," declares Theodore P. Labuza, professor of food science and engineering at the University of Minnesota. "These products are going to be put out in the produce section," he says, adding that "there's going to be a time when consumers are confused—are they buying food or a drug?"

Such claims could lead to confusion for consumers as early clinical and epidemiological studies report conflicting or confusing results. Labuza points to one study that reported that large volumes of beer are beneficial because of antioxidants in the hops. Another study concluded that voluminous amounts of coffee help to prevent cirrhosis of the liver. "It made me wonder if I should put my money into companies that make urinals," Labuza says.

But the foods also give doctors a potential tool. "The physician's prescription to lower cholesterol may read: 'Take these pills once a day and eat some stanol ester–containing yogurt for breakfast and lunch,' " Labuza says.

Although food will change, our nutritional requirements will not. Humans will always need protein, the stuff of our muscles, organs and other tissues. Chicken, beef and pork could continue to be our main sources, but many experts foresee a growing market share for others.

Protein powders, for example, are among the big sellers in the previously mentioned sports supplement category. Whey protein isolate has become popular in recent years, thanks to greatly improved methods of manufacture. Basically, whey is what remains of milk when its other main solid components, fat and casein, are coagulated into cheese curd. It was essentially a waste product of cheese making until someone noticed that it was extraordinarily high in protein and extremely low in fat and in lactose, which some people find irritating to the stomach.

Soy: It's What's for Dinner

THE ADVANTAGES OF POWDERS notwithstanding, it is hard to imagine most people doing without protein with more traditional textures. Some nutritionists see fish as the protein staple of the future. But Irena Chalmers, a food writer and professor at the Culinary Institute of America in Hyde Park, N.Y., is betting on soy. "It can be made into anything: any taste, any texture—crunchy or bland or squishy or slimy. It's going to be an enormous tool," she maintains.

As for animal protein, Morris A. Benjaminson has a dream: producing it without the animal. Benjaminson, a biology professor at the Touro College School of Health Sciences and president of Zymotech Enterprises in Bay Shore, N.Y., hopes to turn stem cells into meat. While working on a system to grow edible mushrooms from human waste for long-duration space missions, he recalls that "it occurred to me that not all astronauts will want to be vegetarians" (to say nothing of eating those mushrooms). A chicken coop in the cargo bay was obviously out of the question, so he came up with another idea: growing animal skeletal muscle tissue—a fillet or steak, in other words—in small chambers.

Benjaminson and his team have extracted stem cells from fish embryos and used them to grow muscle cells by stimulating them electrically, mechanically, hormonally and nutritionally. With enough tinkering and funding, Benjaminson thinks that soon he will be able to grow something that has the consistency and taste of filet mignon. So far he has worked mainly with fish muscle cells and has had some limited success in producing a tiny mass of tissue that looks, smells and cooks like a fish fillet. He believes that such a technique could mass-produce boneless chicken breasts for a fraction of the cost of a commercial chicken farm, without the salmonella and other harmful organisms that can exist on supermarket poultry.

Benjaminson is not the only one working in the field. Dutch researchers at Utrecht University are using pig stem cells to produce vat-grown pork. They hope to create minced meat that could be used in burgers, sausages and pizza toppings within the next couple of years.

Jason Matheny, a University of Maryland doctoral student who directs the nonprofit group New Harvest, envisions "meat sheets" composed of layers of animal muscle and fat

IN A LABORATORY in Bay Shore, N.Y., researchers led by Morris A. Benjaminson (*above*) are sustaining fish muscle cells and even growing modest amounts of new muscle cell components outside of a fish. The dark streak in the image at the left is a tiny sample of fish muscle; it is surrounded by fibroblast cells, a major component of connective tissue. Ultimately the work could lead to a synthetic fish fillet sandwich.

MARK HAVEN (*top*); MORRIS A. BENJAMINSON (*bottom*)

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cells. He believes that using inexpensive nutrients from plant or fungal sources could drive the price of vat-grown meat down to as little as $1 a pound. It could even be improved through the addition of omega-3 fatty acids and other heart-healthy ingredients.

Will vat-grown meat produce philosophical conundrums? Many vegetarians adopt the lifestyle for health reasons, but others do so because they object to exploitation of animals for food. "No animal is harmed here. This stuff is pretty much as guilt-free as you can get," says Jack William Bell, a Seattle software engineer and part-time futurist.

He points out that the technology could give rise to unexpected culinary choices. "Endangered species might no longer be taboo," Bell suggests. "What if we used cultures from endangered or even extinct species? Would it be okay to have Siberian tiger on a stick? Spotted owl nuggets? You could have that bowl of panda stew in good conscience!"

Clearly, in a world where a steak might come from a cow or a test tube and a head cold might be treated with a pill or a salad dressing, the consumer is going to need a little more help. Fortunately, grocery stores are becoming more interactive, with help not only for the confused but also for the harried.

Keeping It Fresh

IT IS UNLIKELY that on the shelves of tomorrow's high-tech, user-friendly grocery stores the tastier, healthier wares will be offered in the same old stifling packaging and wrappings used today. Take romaine lettuce. We've all seen its mysterious transformation: from a crisp, light delight to the taste buds to a repulsive sack of foul, brown goo after a couple of weeks in a standard plastic bag. Not so in the future, Labuza says.

The trouble with storing a head of lettuce in a garden-variety plastic bag is that the lettuce is still alive, taking in oxygen from its surroundings and using it to convert stored sugars to energy for growth and metabolism. In short order, the supply runs out. "When the oxygen level dips below a certain level, [the lettuce dies and] begins to rot," Labuza explains.

Preservation is best achieved by slowing down respiration, so that the vegetable uses its stores more slowly and lives longer. That depends in part on maintaining the oxygen level of the bag at an optimum level—lettuce stays crisp in an atmosphere of about 3 percent oxygen. The goal for the plastics industry is to produce a bag that takes in oxygen ("respires") at precisely the same rate that the vegetable or fruit does. Polymer scientists have already made some progress in this area. River Ranch Fresh Foods in Salinas, Calif., markets to growers a line of produce bags that have variable permeabilities to carbon dioxide and oxygen. The bags can increase shelf life up to 100 percent, depending on the fruit or vegetable, according to Sannai Gong, R&D manager at River Ranch.

Another approach is a new technology called SmartFresh. Marketed by AgroFresh in Spring House, Pa., the active ingredient neutralizes the effect of a natural gas called ethylene, which prompts fruit to ripen. By negating ethylene's effects, SmartFresh delays ripening and significantly increases a fruit's shelf life.

But ambient gases are only part of the problem. Meat doesn't last long in the presence of bacteria, and pathogens such as salmonella and some strains of *Escherichia coli* present a real hazard to consumers. One solution—irradiating food with high-energy particles—kills bacteria quickly and efficiently. Although the procedure has met with some consumer resistance, Connelly expects it to become an important technology. He envisions underground vaults filled with radioactive materials, rather like a walk-in x-ray machine: "You could drop in whole packaged food products and have them emerge stable," he asserts.

But if high-energy particles don't appeal, perhaps high pressure is more palatable. Although no one is quite sure how it works, Labuza says that pressures of 240 to 275 kilopascals (35 to 40 pounds per square inch) efficiently sterilize packaged food, apparently killing pathogenic bacteria by disrupting the function of DNA. "You take guacamole, put it in a plastic package and put it in a cylinder, fill it with water, and then use a piston to pressurize the whole system. In a matter of minutes, you can kill most of the spoilage and food-poisoning organisms," Labuza says.

Once sterilized, the food could be shielded from outside contamination by shrink-wrapped packaging with antibacterial molecules incorporated right into it. Thus sequestered, food should be well preserved from microbiological hazards, but it faces one other challenge: oxygen can infiltrate the packaging and cause it to become rancid. To block it, packagers have added "oxygen traps"—in some cases simply iron—that react with oxygen before it can attack the contents of the package. The payoff is packages of meat that could last several years unrefrigerated.

Whatever the future may bring, it seems certain to end the refrigerator biology projects that greet most returning travelers today. Slimy vegetables, rancid meat and nutritionally bankrupt starches could also be eliminated. And test-tube chicken could be the main course.

Will our taste buds be titillated? Or will manufacturers get caught up in a frenzy and make the same mistakes soy food producers made in the 1970s, sacrificing everything—including taste—for the sake of health benefits? Let's hope they do not, or the food of the future might be old-fashioned carry-out cheeseburgers and fries. SA

Vat-grown meat could give rise to unexpected culinary choices. Endangered species might no longer be taboo.

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RESEARCHERS inspect genetically modified corn in a research greenhouse. In 2005, 52 percent of the U.S. corn crop was genetically modified, according to the National Agricultural Statistics Service.

WOLFGANG FLAMISCH *zefa/Corbis*

The Risks on the Table

By **Karen Hopkin**

More than half the foods in U.S. supermarkets contain genetically modified ingredients. Have they been proved safe for human consumption?

A farmworker crouches in the hot Texas sun, harvesting celery for market. That evening, painful red blisters erupt across his forearms. The celery—a newly developed variety prized for its resistance to disease—unexpectedly produces a chemical able to trigger severe skin reactions.

Traditional breeding methods generated this noxious vegetable. But opponents of genetically modified foods worry that splicing foreign genes (often from bacteria) into food plants through recombinant-DNA technology could lead to even nastier health surprises. The stakes are high: GM foods are sold in many countries. In the U.S., an estimated 60 percent of processed foods in supermarkets—from breakfast cereals to soft drinks—contain a GM ingredient, especially soy, corn or canola.

Detractors cite several reasons for concern. Perhaps proteins made from the foreign genes will be directly toxic to humans. Maybe the genes will alter the functioning of a plant in ways that make its food component less nutritious or more prone to carrying elevated levels of the natural poisons that many plants contain in small amounts. Or perhaps the modified plant will synthesize proteins able to elicit allergic reactions.

Allergy was the big worry in 2000 when StarLink corn—genetically modified to produce an insecticidal protein from the bacterium *Bacillus thuringiensis* (Bt)—turned up in taco shells, corn chips and other foods. StarLink had been planted after receiving approval for use in animal feed, but concerns about the potential allergenicity of its particular version of the Bt protein kept the corn from gaining approval for human consumption. Although U.S. regulators found no cases of allergic reaction that could be attributed to the consumption of food containing small amounts of StarLink corn, the product was removed from the market.

Proponents offer a number of defenses for genetically engineered foods. Inserting carefully selected genes into a plant is safer than introducing thousands of genes at once, as commonly occurs when plants are crossbred in the standard way. GM crops designed to limit the need for toxic pesticides can potentially benefit health indirectly, by reducing human exposure to those chemicals. More directly, foods under study are being designed to be more nutritious than their standard counterparts. Further, GM crops that produce extra nutrients or that grow well in poor conditions could provide critical help to people in developing nations who suffer from malnutrition.

Advocates note, too, that every genetically engineered

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food crop has been thoroughly tested for possible health effects. Relatively few independent studies have been published, but manufacturers have conducted extensive analyses, because they are legally required to ensure that the foods they sell meet federal safety standards. Companies voluntarily submit these test results to the U.S. Food and Drug Administration in advance of sale.

The manufacturers' studies typically begin by comparing the GM version under consideration with conventionally bred plants of the same variety, to see whether the addition of a foreign gene significantly alters the GM plant's chemical makeup and nutritional value. If the proteins made from the inserted genes are the only discernible differences, those proteins are checked for toxicity by feeding them to animals in quantities thousands of times higher than humans would ever consume. If the genetic modification leads to more extensive changes, toxicity testers may feed the complete GM food to laboratory animals.

To assess the allergy-inducing potential, scientists check the chemical makeup of each novel protein produced by the genetically altered plant against those of 500 or so known allergens; having a similar chemistry would raise a red flag. Proteins are also treated with acid to mimic the environment they will encounter in the stomach; most known allergens are quite stable and survive such treatment unscathed. Finally, investigators consider the original source of the protein. "There is no way that a peanut gene will ever be allowed into a strawberry," observes Thomas J. Higgins of the Commonwealth Scientific and Industrial Research Organization in Australia: too many people are allergic to proteins in peanuts.

Arguably, the testing system has worked well so far. It showed that the protein in StarLink corn might be allergenic (hence the animal-feed-only approval) and led other products—such as soybeans that contained a protein from Brazil nuts—to be abandoned before they had a chance to hit grocery shelves. "I don't know of any evidence that any product on the market is unsafe," says Peter Day, professor emeritus of genetics at Rutgers University.

The safety tests are not necessarily foolproof, though. For example, GM plants often cannot make enough of the foreign protein for use in feeding studies. So researchers have bacteria churn out the proteins. But a protein made by plants, the form people would consume, might be slightly different from the one made by microbes—a difference that might theoretically affect the safety assessment of that protein. And studies using whole GM foods are limited by the amount of any food that can be introduced into an animal's diet without generating nutritional imbalances that can confound the test results. This effect is one reason that scientists have criticized a controversial 1999 study claiming that the foreign DNA in GM potatoes led to abnormalities in the intestinal lining in rats.

Beyond the acute safety considerations, some critics fear that GM foods will do harm more insidiously, by hastening the spread of antibiotic resistance in disease-causing bacteria. When food designers genetically alter a plant, they couple the selected genetic material with a "marker" gene that reveals which plants have taken up foreign genes. Often the marker genes render plant cells resistant to antibiotics that typically kill them. At issue is the possibility that resistance genes might somehow jump from GM foods to bacteria in a consumer's gut, thereby aggravating the already troubling rise of antibiotic resistance among disease-causing bacteria.

The chances of such transfer are reportedly remote—"less likely than winning a national lottery three times in a row," notes Hans Günter Gassen, professor emeritus at the Institute of Biochemistry at the University of Technology in Darmstadt, Germany. Even so, most companies have stopped developing new products that contain antibiotic resistance genes.

Meanwhile many consumers remain disturbed that most safety tests are performed by the very corporations that produce GM foods. Steve L. Taylor, professor of food science and technology at the University of Nebraska, admits that some may view the practice as unseemly. But, he asks, who else should shoulder the burden—and the expense? "I'd rather see the companies spend the money than have the government use my tax dollars," he adds. "I don't care if we're talking about bicycles or GM corn, it's their obligation to prove that their products are safe." No doubt concerned scientists and citizens will continue watching to see that they do so. SA

Detractors cite several reasons for concern. Perhaps proteins made from the foreign genes will be directly toxic to humans. Perhaps GM plants will elicit allergic reactions.

Karen Hopkin is a science writer based in Somerville, Mass.

MORE TO EXPLORE

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GM FOOD SAFETY **Q&A**

Two leading figures in the debate over genetic engineering defend their stances

Interviews by **Sasha Nemecek**

Does the World Need **GM Foods?**

YES

ROBERT B. HORSCH, vice president of international development partnerships at Monsanto Company, received the 1998 National Medal of Technology for his pioneering experiments in the genetic modification of plant cells. He talks about the promise of GM crops.

How did you become interested in the genetic modification of plants?

I started in this field with a strong interest in plants but with what you might call an academic interest in agriculture. I had this vague, naive notion that if we could genetically improve plants with the new tools of molecular biology, we would find a way to make biotechnology relevant to agriculture.

That has now happened. Biotechnology is a great tool that will allow us to produce more food on less land and with less depletion or damage to water resources and biodiversity. I am convinced that biotechnology is not just relevant but imperative for helping us meet the rapidly growing demand for food and other agricultural products. The combination of more people and rising incomes will increase the demand for food by at least 50 percent in the next 25 years.

TOM WOLFF

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But critics of genetically modified foods point out that companies are not going to start giving products away. Can a corporation like Monsanto make biotechnology affordable for farmers in the developing world?

Cultivating commercial markets and applying technology to help the developing world are not mutually exclusive at all. One approach that works very well is to segment the market into different areas. One is the pure commercial market. It makes economic sense, as a for-profit company, for us to invest in products and market developments in places where we can sell our products and where we think we can make a profit. In 2005 more than 90 percent of the 8.5 million farmers who grew biotech crops were small farmers in developing countries. Commercial expansion has been more successful in developing countries than I would have predicted just a few years ago.

Then there's another area, what I call a transitional market, where we have less experience related to biotechnology but that in the long run I think may be more powerful and beneficial for development efforts. We have used this approach with our older, nonbiotech products, such as high-yielding corn hybrids, and I think we can use it in the future with biotech products. Small farmers can see results in a demonstration plot and, if they want, try it themselves on a portion of their farm. If it works for them, they can expand or repeat it the next year. We have programs like this in Mexico, India and parts of Africa. By the third or fourth year, if it's working, the farmers will have made enough money from the experimentation phase to be able to run essentially on their own.

And what about profits for Monsanto?

We sell the seeds and the herbicide at market prices, and we subsidize the learning, the testing and the development of distribution chan-

nels so that we don't actually make a profit in the first several years. Only if the project is successful enough to become self-sustaining will we start making a profit. As of 2006, our cooperative development projects in Mexico, India and South Africa have successfully transitioned to self-sustaining markets for Monsanto and for farmers. In sub-Saharan Africa, the products are working well in farmers' hands, but the regulatory capacity and market infrastructure are developing more slowly and still need cooperative help.

Let's turn to the environmental effects of GM crops. What do you consider the most important benefits of the technology?

Lower use of pesticides is the environmental benefit that people relate to immediately, and it's huge for a product like Bt cotton. [*Editors' note: Bt crops have been genetically modified to produce a bacterial protein that kills certain insect pests.*] According to a recent report, 380 million pounds of pesticides were not used in the U.S. between 1996 and 2004 as a result of insect-protected crops, and many, many more won't be used in the future as biotech expands in acreage and in traits.

Beyond that there are also yield benefits. The Bt corn we have today doesn't displace a whole lot of insecticides, but what it does do is boost the yields by a noticeable margin. It depends on the year and on the region, but the increase in yield can range from 5 to 15 percent. You get a greater corn harvest with the same resources that you were going to use anyway.

Getting more from really good farmland, then setting aside land that is of marginal quality and returning it to habitat for wildlife is very beneficial to the environment. We can't continue to indefinitely expand our old practices—of chemical use, of water diversion, of plowing wild lands and converting them to farms, of nonagricultural sprawl, and of the production of industrial waste.

One of the benefits of biotech that we first heard about was nutritionally enhanced foods. But despite promises of healthier broccoli, we have Bt corn. The famous "golden rice" is not available to consumers yet and is still in the early stages of testing. Will we ever have nutritionally enhanced foods?

We're seeing progress across industry, academia and the nonprofit community. Efforts are under way to modify fatty acids to make vegetable oils more healthy for consumers. Monsanto and other companies have commercialized healthier oils derived from conventional breeding and are on track to commercialize improved biotech oils early in the next decade. These healthier oils are designed to produce foods with very low levels of saturated fats. Further research involves ways to produce food crops enriched with omega-3 fatty acids beginning early next decade. These products, including a biotech oilseed, would provide consumers with additional ways to improve heart health. The goal of this project is to create an affordable, land-based, renewable oil source with properties that make it easier to create great-tasting food products than current alternatives.

Efforts to produce nutritional enhancements from biotechnology have been ongoing. But more work is under way at a scale that should lead to success. For instance, the global initiative known as Harvest Plus is using both conventional breeding and biotechnology to increase levels of iron, zinc and vitamin A in beans, cassava, maize, rice, sweet potatoes and wheat.

Monsanto has been one of the most criticized, even despised, corporations because of its role in the development of genetically modified foods. Has it ever been hard to tell people you're an employee of Monsanto?

I've had a few people react negatively, but my experience is that when people meet you as a person, their reactions are very different than when they are commenting on the big nameless, faceless company.

I think the company is making an effort to address people's concerns about GM foods more openly. We've recognized that some genetic modifications are particularly bothersome. Among vegetarians, for instance, the idea of eating a vegetable that has an animal gene in it might raise questions. For certain cultures or religious groups, there could be similar concerns. So we decided it was better to avoid using animal genes in food crops.

I don't think it serves anybody's interest—including Monsanto's—to discount the potential risks of biotechnology. But for where we are today, and for what I see in the pipeline for the next few years, I really don't see a measurable risk from the GM products we are selling or developing. There have been numerous national and international scientific organizations that have reached this same conclusion, including the American Medical Association, the National Academy of Sciences, the World Health Organization and many others.

The year 2005 marked the tenth anniversary of large-scale cultivation of biotech crops, with more than a billion cumulative acres of production. Twenty-one countries—including Spain, Germany, Portugal, France and the Czech Republic—are commercially growing biotech crops. Benefits have been well documented, and measurable risks have not been found. Given limited farmland and the need to protect natural lands, it is critically important to increase food productivity on a per-acre basis, through advanced breeding and biotechnology.

The first generation of biotech crops has provided significant economic, environmental and grower benefits, and the next generation of biotech crops will provide much broader benefits. Some of these products include crops with improved tolerance to drought, more effective utilization of nitrogen, increased yield and enhanced nutrition.

We at Monsanto have pledged to listen better to and engage in dialogue with concerned groups, to be more transparent in the methods we use and the data we have about safety, to respect the cultural and ethical concerns of others, to share our technology with developing countries, and to make sure we deliver real benefits to our customers and to the environment. I think this new attitude and new set of commitments will help improve both our company's image and the acceptance of this new technology.

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Does the World Need **GM Foods?**

NO

MARGARET MELLON, director of the food and environment program of the Union of Concerned Scientists in Washington, D.C., holds a law degree and a Ph.D. in molecular biology. She explains her concerns about the effects of GM foods on human health and the environment.

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How did you become interested in genetically modified foods?

I became aware of genetic engineering while running a program on toxic chemicals at the Environmental Law Institute in the 1980s. I was initially more positively disposed toward biotechnology than I came to be over the years. Like a lot of folks, I wasn't very critical. But the more I knew about the technology and the deeper the questions I asked about it, the less likely I was to accept at face value the extravagant promises made on its behalf.

I should also say, however, that my colleagues and I at the Union of Concerned Scientists are not opposed to biotechnology. We think its use in research and drug manufacture, for example, is essential. The therapeutic benefits of the new drugs outweigh the risks, and often there aren't any alternatives. But in agriculture, it's different. So far, at least, there are only modest benefits associated with biotechnology products, and it has yet to be shown that the benefits outweigh the risks. And there are exciting alternatives to solving agricultural problems that we are simply ignoring.

Agriculture isn't like medicine. We in the U.S. produce far more food than we need. And we are so wealthy that whatever we can't produce we can buy from somebody else. As a result, there are about 300,000 food products on our grocery shelves and 10,000 new ones added every year. The notion that consumers in the U.S. fundamentally need new biotechnology foods isn't persuasive.

But of course, many scientists and policy experts argue that *we do* need biotechnology to feed the world, especially people in the developing world.

That is an important question to ask because so many people—more than 800 million—are undernourished or hungry. But is genetic engineering the best or only solution? We have sufficient food now, but it doesn't get to those who need it. Most hungry people simply can't afford to buy what's already out there even when commodity prices are at all-time lows. How does genetic engineering address the problem of income disparity?

The real tragedy is that the debate about biotechnology is diverting attention from solving the problem of world hunger. I'd like

TOM WOLFF

to see people seriously asking the question, "What can we do to help the world's hungry feed themselves?" and then make a list of answers. Better technology, including genetic engineering, would be somewhere on the list, but it would not be at the top. Trade policy, infrastructure and land reform are much more important, yet they are barely mentioned.

Genetic engineering has a place and should not be taken off the table, but I don't believe it is a panacea for world hunger. Treating it as if it is distorts this important debate. It is also amazing to me how quickly some have dismissed the virtues of traditional breeding—the technology that, after all, made the U.S. into an agricultural powerhouse.

Can we turn to another potential benefit that people claim for GM foods: agriculture that is more environmentally friendly?

Let's ask a question: What is a green agriculture? Is it one that doesn't depend on pesticides? I think it's a lot more than that, actually. But if we just consider avoiding pesticide use, we now have some data on the impacts of engineered crops. Surveys of American farmers by the Department of Agriculture show that the use of Bt [pest-resistant] corn aimed at the corn borer, for example, hasn't done much to reduce the application of pesticides to corn, because the vast majority of corn acreage isn't treated with pesticide to control that pest.

The introduction of Bt cotton, however, has resulted in a measurable drop in pesticide use. That's good for the environment and good for the farmers who cut their input costs. But this benefit will last only as long as the Bt trait keeps working. I think most scientists expect that the way Bt crops are being deployed will eventually lead to the evolution of resistance in the target pests, which means that the Bt cotton won't work anymore. We are likely to run through Bt cotton just like we ran through all the pesticides before it. So it isn't a durable path to a greener agriculture.

And there are environmental risks out there. Most scientists agree now that gene flow will occur—genes *will* go from engineered crops to nearby relatives. That means pollen will carry novel genes from the agricultural settings into neighbors' fields or into the wild. Widespread use of GM crops has already led to the creation of herbicide-resistant weeds in Canada and the U.S.

What about the health risks of GM foods? Do you see any looming problems?

I know of no reason to say the foods currently on the market are not safe to consume. But I don't have as much confidence as I should in that statement. There was a letter published in the journal *Science* a few years ago from someone who had searched the literature for peer-reviewed studies comparing GM food to non-GM food. The researcher found something like five studies, a situation that persists to this day. That's not enough of a basis, from a scientific standpoint, to assure ourselves that these foods are safe.

I would say the biggest concern is the possibility of converting nonallergenic foods into allergens. Introducing new toxins into food is also a risk. Of course, breeders are going to try to avoid doing that, but plants have lots of toxins in them; as scientists manipulate systems that they don't completely understand, one of the unexpected effects could be turning on genes for toxins. There are rules that govern how genes come together and come apart in traditional breeding. We're not obeying those rules.

So you don't see genetic engineering of crops to be an extension of traditional breeding?

No, not at all. You just can't get an elephant to mate with a corn plant. Scientists are making combinations of genes that are not found in nature.

From a scientific standpoint, there is no dispute that this is fundamentally different from what has been done before. And that it is unnatural. Now, because it's new and unnatural doesn't *necessarily* mean that it will prove to be more risky. But it is certainly a big enough break with what we have done before to demand an extra measure of caution.

And caution is particularly appropriate where the technology involves our food supply. Lots and lots of people—virtually the whole population—could be exposed to genetically engineered foods, and yet we have only a handful of studies in the peer-reviewed literature addressing their safety. The question is, Do we *assume* the technology is safe based on an argument that it's just a minor extension of traditional breeding, or do we *prove* it? The scientist in me wants to prove it's safe. Why rest on assumptions when you can go into the lab?

Science can never prove that any technology is 100 percent safe. Will you ever be satisfied that we've tested GM foods enough? And how much risk is acceptable?

Sure, I could be satisfied that GM foods have been adequately tested. But it's premature to address that question now. Nobody is saying, "Look, we've got this large body of peer-reviewed experimental data comparing GM with non-GM foods on a number of criteria that demonstrate the food is safe."

When we have generated such a body of evidence, *then* there will be an issue of whether what we have is enough. And eventually, if things go well, we'll get to a point where we say, "We've been cautious, but now we're going to move ahead." But we're nowhere near that point now.

Obviously, we take risks all the time. But why are we taking these risks? If we didn't have an abundant food supply, if we didn't have something like 300,000 food products on our shelves already, then we would have an argument for taking this society-wide risk. But we've got plenty of food. In fact, we've got too much. And although we have many problems associated with our food system, they are not going to be solved by biotechnology. SA

Sasha Nemecek, a former staff editor at Scientific American, *is a science writer based in New York City.*

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Seeds of Concern

By **Kathryn Brown**

Are genetically modified crops an environmental dream come true or a disaster in the making? Scientists are looking for answers

How is your genetically modified diet going? If you ate cereal, drank soda, munched baked snacks or used cooking oil this week, you very likely ate some engineered protein—now a staple of American fare.

During the past decade the amount of farmland devoted to genetically modified (GM) crops has increased more than 50-fold, to an estimated 222 million acres worldwide in 2005, according to the International Service for the Acquisition of Agri-Biotech Applications (ISAAA). The U.S. grows more than half this biotech harvest, followed by 20 additional countries. Today's top crops: soybeans, corn, cotton, and canola modified to tolerate specific herbicides or resist certain insects. Tomorrow new GM crops might withstand drought, resist viruses, grow bigger, yield pharmaceuticals and do other things nature never imagined.

But it is not all sunshine and sweet profit for GM farming. Controversy—and confusion—over the technology remains.

A. HUBER AND U. STARKE *zefa/Corbis*

SOYBEANS are the most common genetically modified crop, covering almost 135 million acres worldwide in 2005.

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"We haven't had the asparagus that ate Cleveland," says geneticist Norman Ellstrand, director of the Biotechnology Impacts Center at the University of California, Riverside. "But there's been at least one notable event of engineered crop genes escaping from farms or field trials every year—and that doesn't give us comfort."

And GM crops suffer other growing pains. Their measurable benefit—in reduced pesticide use or increased yield—varies considerably, depending on the technology, crop and region. Moreover, preliminary research indicates that at least one kind of GM cotton is losing ground against pests. Finally, public debate over GM foods continues, pitting state and local legislatures—and sometimes entire countries—against each other. As Jane Rissler, deputy director of the food and environment program at the Union of Concerned Scientists, puts it: "From where I sit, genetically modified crops are not a slam dunk."

Three Worries

1 **Superweeds will arise** as genes that give crops the ability to kill insect pests or to withstand herbicides find their way into weeds.

What the research says:
Researchers recently found accidental release of GM grass genes into wild grasses in Oregon. Such incidents could pose serious problems both in the U.S. and in regions where GM crops have weedy relatives.

2 **GM crops will fail** because insect pests will evolve tolerance to, or somehow overcome, built-in insecticides.

What the research says:
Studies have not demonstrated insect tolerance, but a preliminary survey of farmers in China suggests that secondary pests unaffected by Bt gene modification are damaging Bt cotton crops.

3 **Innocent creatures will be hurt** by insecticides built into many GM crops.

What the research says:
Based on field and lab tests, the Environmental Protection Agency has determined that current GM crops engineered with insect resistance or herbicide tolerance do not pose unreasonable risks to the environment.

A Modified Farmscape

IT ALL BEGAN with business. Although relatively small compared with other agricultural product markets, the commercial seed market in the U.S. (about $5.7 billion) and worldwide (about $25 billion) is rapidly growing, particularly for major field crops, according to the U.S. Department of Agriculture. Fewer than half a dozen companies dominate the domestic seed market, and as biotechnology emerged, they saw an opportunity to genetically modify crop seeds with one or more desirable traits. Many farmers were willing to pay for premium seeds with these traits.

Today most GM crops contain genes enabling them to either resist insect pests or tolerate weed-killing herbicides [*see box on page 44*]. The herbicide-tolerant types contain genes enabling them to survive when exposed to broad-spectrum weed killers such as glyphosate (sold as Roundup), potentially allowing farmers to forgo more toxic chemicals that target specific weed species. The insect-resistant varieties of GM crops make their own insecticide, a property meant to reduce the need for chemical sprays. To date, insect resistance has been provided by a gene from the soil bacterium *Bacillus thuringiensis* (Bt). This gene directs cells to manufacture a crystalline protein that is toxic to certain insects—especially caterpillars and beetles that gnaw on crops—but does not harm other organisms.

In 2005 herbicide-tolerant varieties represented 87 percent of the U.S. soybean crop and 61 percent of the cotton crop. That same year Bt varieties represented 35 percent of the U.S. corn crop.

These crops have shown clear benefit, says Zigfridas Vaituzis, a senior scientist at the Environmental Protection Agency. "With herbicide-tolerant crops, farmers can spray their fields with relatively safe, biodegradable chemicals," Vaituzis says. "For its part, Bt cotton has cut pesticide use on cotton crops by half. A conventional cotton crop may take 12 applications of various pesticides each season. Halving that means less exposure to those chemicals, both on the farm, in groundwater and in spray drift in the surrounding community. Those are measurable benefits."

Early environmental fears about potential negative effects of Bt corn pollen on monarch butterflies, or of Bt toxins on soil organisms, have not materialized in repeated studies. "We've seen no uptake of Bt toxins by other plants or any effect on soil microbes," says Guenther Stotzky, a soil microbiologist at New York University. "That's why I'm no longer a critic of Bt crops."

A Risky Escape

BUT AT LEAST ONE environmental risk looms: escape. Researchers have long worried that unwitting insects or the right wind could carry GM crop pollen to weedy plant relatives, fertilizing them. The newly endowed plants could then break ecological rank, becoming "superweeds" that push out native plants or resist pesticides.

Until recently, that fear remained fiction, as scientists en-

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gineered farm crops that mostly lack wild, weedy relatives in the U.S. But in August 2006 ecologists at the EPA reported the first wild outbreak of a GM crop: a turfgrass.

In central Oregon the Scotts Miracle-Gro Company had field-tested an herbicide-tolerant variety of creeping bentgrass, for possible use on golf courses. Surveying the nearby area, EPA scientists found wild grass with the genetic modification at six sites, some more than two miles away from the test plots.

Reporting in the journal *Molecular Ecology,* the scientists suggested that wind carried the modified grass's seeds and pollen to the locations where new plants emerged. The USDA has launched an environmental impact assessment of the transgenic grass to determine whether it could spread and become invasive.

The runaway grass alarms scientists, in part because they worry that next-generation GM crops—such as "biopharms," or plants engineered to yield pharmaceuticals—could similarly escape. "When we start growing antigens that could get back into the food chain, this kind of event becomes much more serious," Stotzky says.

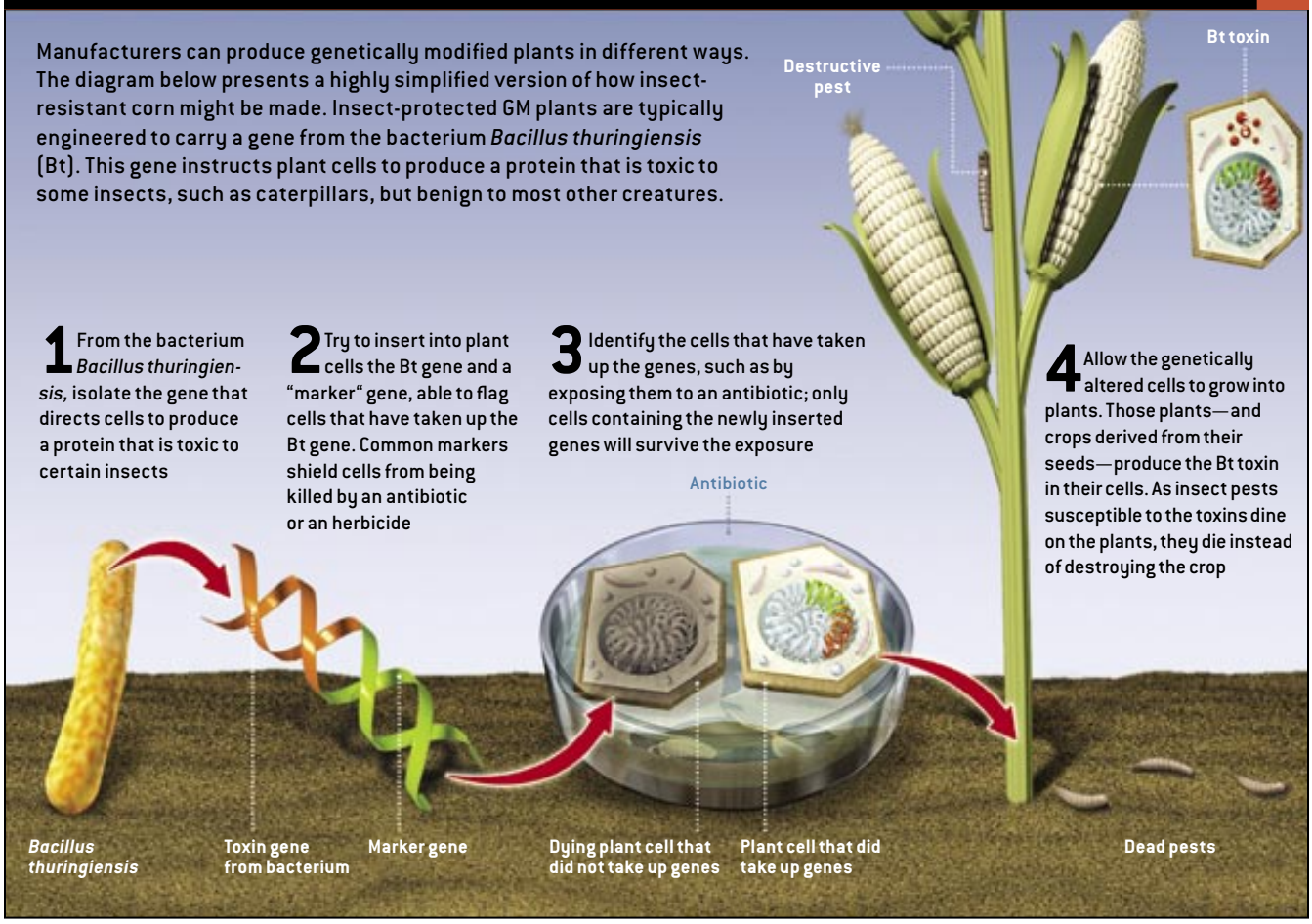
Already the USDA has come under fire for its oversight of biopharming. Four environmental groups have successfully sued the agency over biopharm field trials in Hawaii, in which corn and sugar cane plants were modified to make human hormones and vaccine ingredients to fight HIV and hepatitis B. In August a U.S. District Court judge in Hawaii ruled that the USDA broke national environmental laws by allowing the open-air field trials without first considering their environmental impact, particularly on endangered species. In response, the USDA has overhauled its permit process.

Beyond the field, experimental GM crops have repeatedly found their way into the food supply—twice during the summer of 2006 alone. First, Riceland Foods, the country's largest marketer of rice, discovered trace amounts of an unapproved herbicide-tolerant rice strain in its commercial rice supplies, which are grown across a wide region of the southern U.S. In response, the European Union placed strict testing requirements on U.S. imports, sending U.S. rice prices tumbling and provoking a class-action lawsuit by farmers alleging that Bayer CropScience—which had bred the rice—was negligent in preventing GM seeds from contaminating the nation's seed supply.

Also last summer, the environmental groups Greenpeace and Friends of the Earth reported that their tests of processed

HOW TO MAKE A GENETICALLY MODIFIED PLANT

Manufacturers can produce genetically modified plants in different ways. The diagram below presents a highly simplified version of how insect-resistant corn might be made. Insect-protected GM plants are typically engineered to carry a gene from the bacterium *Bacillus thuringiensis* (Bt). This gene instructs plant cells to produce a protein that is toxic to some insects, such as caterpillars, but benign to most other creatures.


Destructive pest
Bt toxin
1 From the bacterium *Bacillus thuringiensis,* isolate the gene that directs cells to produce a protein that is toxic to certain insects
2 Try to insert into plant cells the Bt gene and a "marker" gene, able to flag cells that have taken up the Bt gene. Common markers shield cells from being killed by an antibiotic or an herbicide
3 Identify the cells that have taken up the genes, such as by exposing them to an antibiotic; only cells containing the newly inserted genes will survive the exposure
Antibiotic
4 Allow the genetically altered cells to grow into plants. Those plants—and crops derived from their seeds—produce the Bt toxin in their cells. As insect pests susceptible to the toxins dine on the plants, they die instead of destroying the crop
Bacillus thuringiensis
Toxin gene from bacterium
Marker gene
Dying plant cell that did not take up genes
Plant cell that did take up genes
Dead pests

JOE ZEFF

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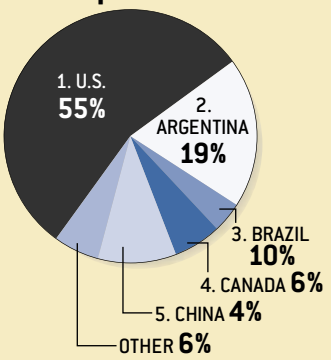
THE LATEST CROP OF NUMBERS

Countries Producing GM Crops in 2005

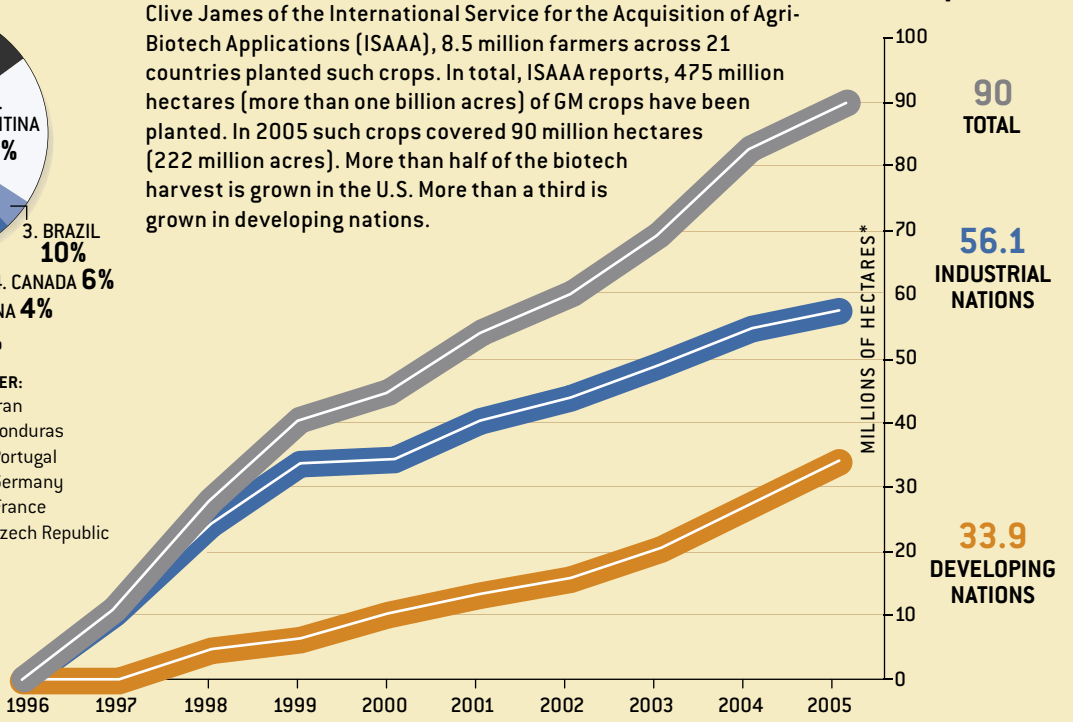


OTHER, IN DESCENDING ORDER:

6. Paraguay
7. India
8. South Africa
9. Uruguay
10. Australia
11. Mexico
12. Romania
13. Philippines
14. Spain
15. Colombia
16. Iran
17. Honduras
18. Portugal
19. Germany
20. France
21. Czech Republic

The year 2005 marked the 10th anniversary of the commercialization of genetically modified (GM) crops. That year, according to Clive James of the International Service for the Acquisition of Agri-Biotech Applications (ISAAA), 8.5 million farmers across 21 countries planted such crops. In total, ISAAA reports, 475 million hectares (more than one billion acres) of GM crops have been planted. In 2005 such crops covered 90 million hectares (222 million acres). More than half of the biotech harvest is grown in the U.S. More than a third is grown in developing nations.

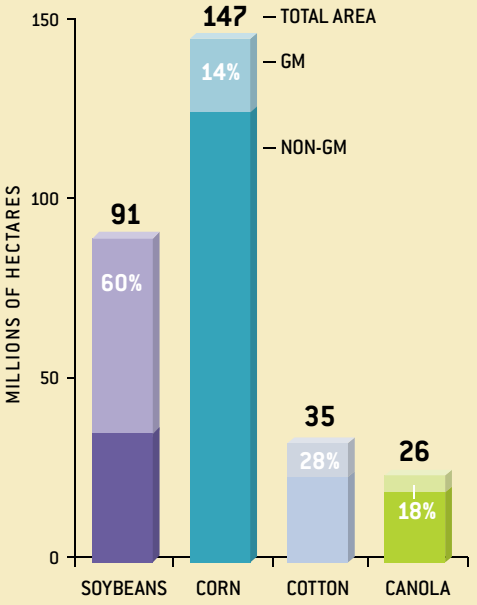
Global Area of GM Crops



**Data were rounded to the nearest 100,000 hectares. 1 hectare = 2.471 acres*

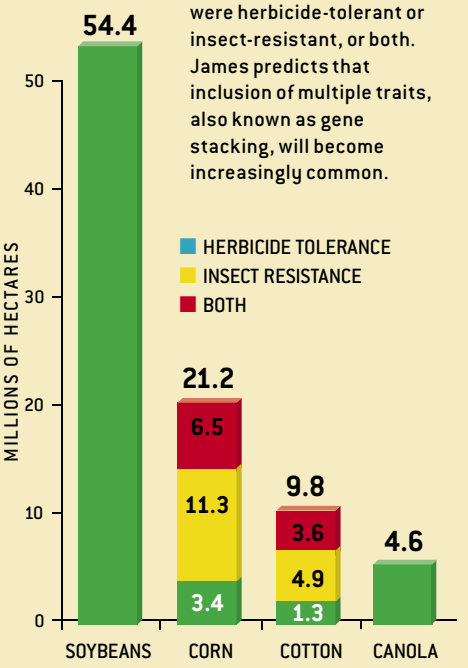
The Most Common GM Crops ...

Soybeans, corn, cotton and canola were the dominant GM crops in 2005, covering 30 percent of the 299 million hectares devoted to these four commodities.

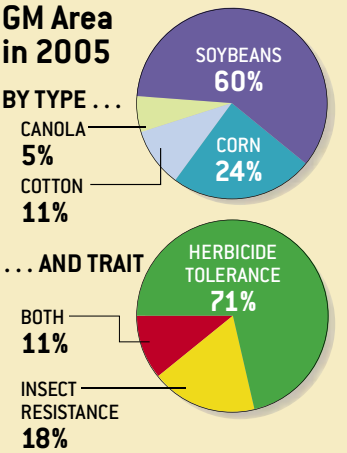


... and How They're Modified

Virtually all GM soybeans and canola planted in 2005 were herbicide-tolerant; corn and cotton were herbicide-tolerant or insect-resistant, or both. James predicts that inclusion of multiple traits, also known as gene stacking, will become increasingly common.



Percent of Total GM Area in 2005



Farmers cultivated other GM crops as well, but these essentially dropped off the data screen when James rounded his figures to the nearest 100,000 hectares. Among them were potatoes, squash, papayas, melons, tomatoes and plants engineered for such traits as virus resistance, delayed spoilage and improved nutrition.

SOURCES: Clive James, ISAAA Briefs No. 34, *Global Status of Commercialized Biotech/GM Crops: 2005;* www.isaaa.org

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rice foods in London had turned up five samples of rice products imported from China, such as vermicelli and rice sticks, containing an unapproved insect-resistant rice variety. The European Commission urged member states to step up controls of GM foods, which are not approved for consumption in Europe.

But that will be difficult to do, Ellstrand says. In an ongoing $1.5-million study funded by the National Science Foundation, he leads a team of biologists and social scientists collaborating to analyze the unintended spread of engineered plant genes. "One serious problem is the frequent disconnect between policymakers, seed salespeople, regulators and farmers about how to grow and control GM crops," Ellstrand explains. As seeds and food cross borders, he adds, that coordination dissolves further.

A Long Lens

WHEN IT COMES TO basic biology, even GM crop proponents worry that gains made by modified plants are only temporary. After all, evolution does not stop for technology. Insects, for instance, may evolve strategies for overcoming Bt technology and eventually consume the transgenic plants with no effect.

Or nature may take a different tack, as suggested by the first long-term economic impact study of Bt cotton in China. That study, presented by Cornell University researchers at the July 2006 meeting of the American Agricultural Economics Association, found that farmers planting Bt cotton—designed to defy the leaf-eating bollworm—initially prospered, cutting pesticide use by 70 percent. By year seven of Bt cotton farming, however, secondary insects such as mirids crept in, replacing the bollworm as the star scourge—and forcing farmers to return to typical spraying levels, even as they paid for Bt seed, which costs two to three times more than conventional seed.

That does not surprise Alison G. Power, an ecology professor at Cornell. "When we breed traditional plants that are resistant to some particular pest, the next most important pest moves in," Power explains. "We see this all the time with plant viruses."

Rebecca Goldburg, a senior scientist at Environmental Defense, predicts that farmers will eventually lose Bt as an effective control against insects and will then move on to another chemical control. "Many of us view this current generation of biotech crops as a kind of diversion, rather than a substantive gain, for agriculture," Goldburg says.

Like scientists, politicians are at odds over GM crops. During the 2005 legislative session, 117 pieces of legislation related to agricultural biotechnology were introduced in 33 states and in the District of Columbia. Many state legislatures attempted to disallow local and county efforts to ban or limit GM seeds and crops. Of the 23 state bills that passed during 2005, two thirds supported GM technology, according to the Pew Initiative on Food and Biotechnology.

More than anything, the public is just plain confused about GM crops, as reported in a survey released in 2005 by the Food Policy Institute at Rutgers University. In the survey of 1,200 U.S. residents, about half said they were unsure or could not take a position on GM foods. Roughly a fourth of them approved of GM technology, but almost as many disapproved. Lead author William Hallman, a Rutgers psychologist, concluded that people "seem to be willing to believe just about anything they hear about GM foods." The study suggests that fewer than half of Americans realize that supermarkets regularly sell GM foods.

Like them or not, GM crops are poised to grow—and not just in the U.S. In 2005, according to the ISAAA, 38 percent of the land planted in GM crops was in developing countries, which desperately need plant varieties that tolerate drought and improve yield, among other traits. In 2006 Iran produced its first full-scale commercial seed supply of Bt rice. China is expected to follow. "Yes, this technology will have to be modified, due to resistance factors, the appearance of new pests and other challenges," Vaituzis says. "But genetically modified crops are here to stay." SA

Even proponents worry that gains made by genetically modified plants are only temporary. After all, evolution does not stop for technology.

THE AUTHOR

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MORE TO EXPLORE

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Edible Vaccines

By **William H. R. Langridge**

One day children may get immunized by munching on foods instead of enduring shots. More important, food vaccines might save millions who now die for lack of access to traditional inoculants

Vaccines have accomplished near miracles in the fight against infectious disease. They have consigned smallpox to history and should soon do the same for polio. By the late 1990s an international campaign to immunize all the world's children against six devastating diseases was reportedly reaching 80 percent of infants (up from about 5 percent in the mid-1970s) and was reducing the annual death toll from those infections by roughly three million.

FOODS UNDER STUDY as alternatives to injectable vaccines include bananas, potatoes and tomatoes, as well as lettuce, rice, wheat, soybeans and corn.

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Being edible, the vaccines would require no syringes—which, aside from costing something, can lead to infections if they become contaminated.

Yet these victories mask tragic gaps in delivery. The 20 percent of infants still missed by the six vaccines—against diphtheria, pertussis (whooping cough), polio, measles, tetanus and tuberculosis—account for about two million unnecessary deaths a year, especially in the most remote and impoverished parts of the globe. Upheavals in many developing nations now threaten to erode the advances of the recent past, and millions still die from infectious diseases for which immunizations are nonexistent, unreliable or too costly.

This situation is worrisome not only for the places that lack health care but for the entire world. Regions harboring infections that have faded from other areas are like bombs ready to explode. When environmental or social disasters undermine sanitation systems or displace communities—bringing people with little immunity (because of disparities in nutrition and health care) into contact with carriers—infections that have been long gone from a population can come roaring back. Further, as international travel and trade make the earth a smaller place, diseases that arise in one locale are increasingly popping up continents away. Until everyone has routine access to vaccines, no one will be entirely safe.

In the early 1990s Charles J. Arntzen and Dominic Man-Kit Lam, then at Texas A&M University, conceived of a way to solve many of the problems that bar vaccines from reaching all too many children in developing nations. Soon after learning of a World Health Organization call for inexpensive, oral vaccines that needed no refrigeration, Arntzen visited Bangkok, where he saw a mother soothe a crying baby by offering a piece of banana. Plant biologists had already devised ways of introducing selected genes (the blueprints for proteins) into plants and inducing the altered, or "transgenic," plants to manufacture the encoded proteins. Perhaps, he mused, plants could be genetically engineered to produce vaccines in their edible parts, which could then be eaten when inoculations were needed.

The advantages would be enormous. The plants could be grown locally, and cheaply, using the standard growing methods of a given region. Because many food plants can be regenerated readily, the crops could potentially be produced indefinitely without the growers having to purchase more seeds or plants year after year. Homegrown vaccines would also avoid the logistical and economic problems posed by having to transport traditional preparations over long distances, keeping them cold en route and at their destination. And, being edible, the vaccines would require no syringes—which, aside from costing something, can lead to infections if they become contaminated.

Efforts to make Arntzen's inspired vision a reality are still quite preliminary. Yet studies carried out in animals over the past 15 years, and small tests in people, encourage hope that edible vaccines can work. The research has also fueled speculation that certain plant-based vaccines might help suppress autoimmunity—in which the body's defenses mistakenly attack normal, uninfected tissues. Among the autoimmune disorders that might be prevented or eased are type I diabetes (the kind that commonly arises during childhood), multiple sclerosis and rheumatoid arthritis.

By Any Other Name ...

REGARDLESS of how vaccines for infectious diseases are delivered, they all have the same aim: priming the immune system to swiftly destroy specific disease-causing agents, or pathogens, before the agents can multiply enough to cause symptoms. Classically, this priming has been achieved by presenting the immune system with whole viruses or bacteria that have been killed or made too weak to proliferate much.

On detecting the presence of a foreign organism in a vaccine, the immune system behaves as if the body were under attack by a fully potent antagonist. It mobilizes its various forces to root out and destroy the apparent invader—targeting the campaign to specific antigens (proteins recognized as foreign). The acute response soon abates, but it leaves behind sentries, known as "memory" T and B cells, that remain on alert, ready to unleash whole armies of defenders if the real pathogen ever finds its way into the body. Some vaccines provide lifelong protection; others (such as those for cholera and tetanus) must be readministered periodically.

Classic vaccines pose a small but troubling risk that the vaccine microorganisms will somehow spring back to life, causing the diseases they were meant to forestall. For that reason, vaccine makers today favor so-called subunit preparations, composed primarily of antigenic proteins divorced from a pathogen's genes. On their own, the proteins have no way of establishing an infection. Subunit vaccines, however, are expensive, in part because they are produced in cultures of bacteria or animal cells and have to be purified out; they also need to be refrigerated.

Plant-based vaccines are like subunit preparations in that they are engineered to contain antigens but bear no genes that would enable whole pathogens to form. Fifteen years ago Arntzen understood that edible vaccines would therefore be as safe as subunit preparations while sidestepping their costs

HITOSHI NISHIMURA *Taxi Japan/Getty Images (preceding pages)*

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Fruitful Research

TOMATO PLANTS AND BANANA TREES growing at the Boyce Thompson Institute for Plant Research at Cornell University have been genetically engineered to produce vaccines in their fruit. Bananas are particularly appealing as vaccines because they grow widely in many parts of the developing world, can be eaten raw and are liked by most children.

FOREST McMULLIN

and demands for purification and refrigeration. But before he and others could study the effects of food vaccines in people, they had to obtain positive answers to a number of questions. Would plants engineered to carry antigen genes produce functional copies of the specified proteins? When the food plants were fed to test animals, would the antigens be degraded in the stomach before having a chance to act? (Typical subunit vaccines have to be delivered by injection precisely because of such degradation.) If the antigens did survive, would they, in fact, attract the immune system's attention? And would the response be strong enough to defend the animals against infection?

Additionally, researchers wanted to know whether edible vaccines would elicit what is known as mucosal immunity. Many pathogens enter the body through the nose, mouth or other openings. Hence, the first defenses they encounter are those in the mucous membranes that line the airways, the digestive tract and the reproductive tract; these membranes constitute the biggest pathogen-deterring surface in the body. When the mucosal immune response is effective, it generates molecules known as secretory antibodies that dash into the cavities of those passageways, neutralizing any pathogens they find. An effective reaction also activates a systemic response, in which circulating cells of the immune system help to destroy invaders at distant sites.

Injected vaccines initially bypass mucous membranes and typically do a poor job of stimulating mucosal immune responses. But edible vaccines come into contact with the lining of the digestive tract. In theory, then, they would activate both mucosal and systemic immunity. That dual effect should, in turn, help improve protection against many dangerous microorganisms, including the kinds that cause diarrhea.

Those of us attempting to develop plant-based vaccines place a high priority on combating diarrhea. Together the main causes—the Norwalk virus, rotavirus, *Vibrio cholerae* (the cause of cholera) and enterotoxigenic *Escherichia coli* (a toxin-producing source of "traveler's diarrhea")—account for some three million infant deaths a year, mainly in developing nations. These pathogens disrupt cells of the small intestine in ways that cause water to flow from the blood and tissues into the intestine. The resulting dehydration may be combated by delivering an intravenous solution of electrolytes, but it often turns deadly when rehydration therapy is not an option. No vaccine practical for wide distribution in the developing nations is yet available to prevent these ills.

By 1995 researchers attempting to answer the many questions before them had established that plants could indeed manufacture foreign antigens in their proper conformations. For instance, Arntzen and his colleagues had introduced into tobacco plants the gene for a protein derived from the hepatitis B virus and had gotten the plants to synthesize the protein. When they injected the antigen into mice, it activated the same immune system components that are activated by

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Volunteers who ate pieces of peeled, raw potatoes containing a benign segment of the *E. coli* toxin displayed immune responses.

the virus itself. (Hepatitis B can damage the liver and contribute to liver cancer.)

Green Lights on Many Fronts

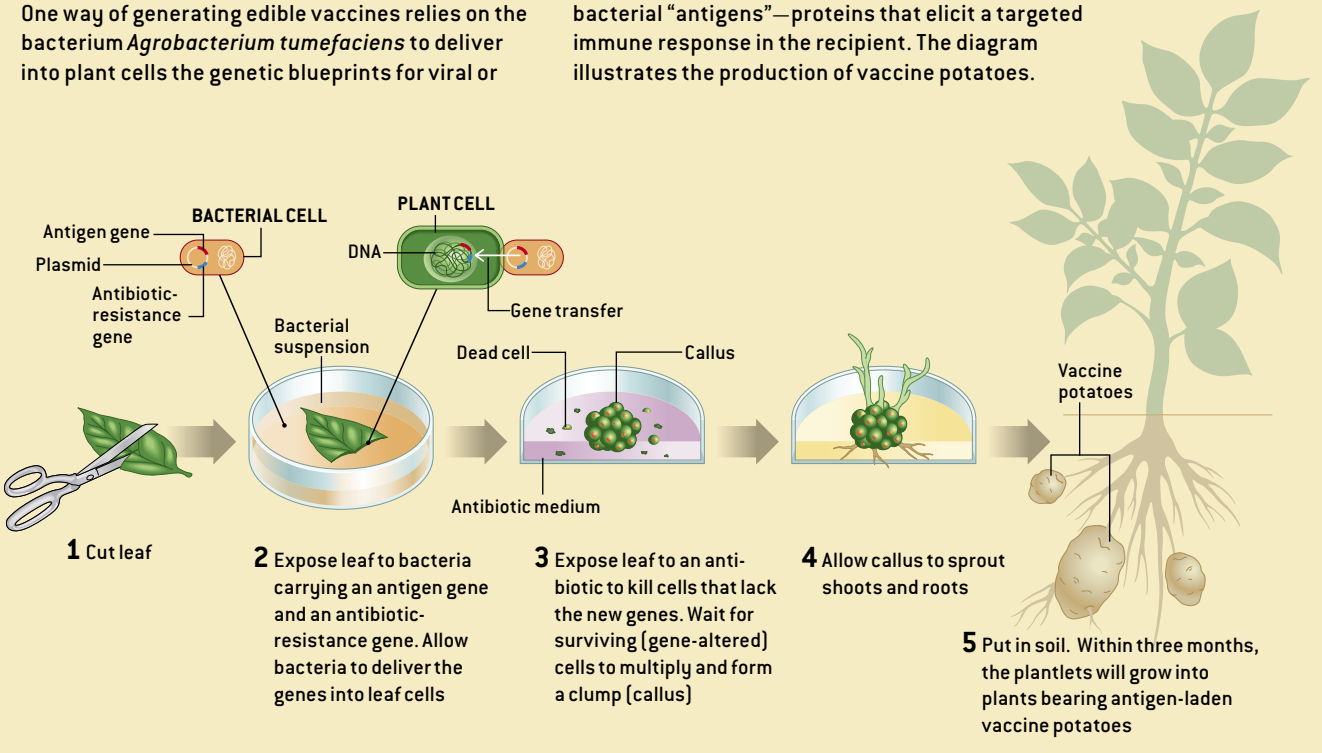
BUT INJECTION is not the aim; feeding is. In the past 10 years experiments conducted by Arntzen, now at Arizona State University, and his collaborators and by my group at Loma Linda University have demonstrated that tomato or potato plants can synthesize antigens from the Norwalk virus, enterotoxigenic *E. coli, V. cholerae,* rotavirus, HIV, anthrax, shigella and the hepatitis B virus. Moreover, feeding antigen-laced tubers or fruits to test animals can evoke mucosal and systemic immune responses that fully or partly protect animals from subsequent exposure to the real pathogens or, in the case of *V. cholerae* and enterotoxigenic *E. coli,* to microbial toxins. Edible vaccines have also provided laboratory animals with some protection against challenge by the rabies virus, *Helicobacter pylori* (a bacterial cause of ulcers) and the mink enteric virus (which does not affect humans).

It is not entirely surprising that antigens delivered in plant foods survive the trip through the stomach well enough to reach and activate the mucosal immune system. The tough outer wall of plant cells apparently serves as temporary armor for the antigens, keeping them relatively safe from gastric secretions. When the wall finally begins to break up in the intestines, the cells gradually release their antigenic cargo.

Of course, the key question is whether food vaccines can be useful in people. The era of clinical trials for this technology is just beginning. Nevertheless, Arntzen and his collaborators obtained reassuring results in the first published human trial, involving about a dozen subjects. In 1997 volunteers who ate pieces of peeled, raw potatoes containing a benign segment of the *E. coli* toxin (the part called the B subunit) displayed both mucosal and systemic immune responses. Since then, the group has also seen immune reactivity in 19 of 20 people who ate a potato vaccine aimed at the Norwalk virus. Similarly, after Hilary Koprowski of Thomas Jefferson University fed transgenic lettuce carrying a hepatitis B antigen to three volunteers, two of the subjects dis-

HOW TO MAKE AN EDIBLE VACCINE

One way of generating edible vaccines relies on the bacterium *Agrobacterium tumefaciens* to deliver into plant cells the genetic blueprints for viral or bacterial "antigens"—proteins that elicit a targeted immune response in the recipient. The diagram illustrates the production of vaccine potatoes.


BACTERIAL CELL
Antigen gene
Plasmid
Antibiotic-resistance gene
PLANT CELL
DNA
Gene transfer
Bacterial suspension
Dead cell
Callus
Antibiotic medium
Vaccine potatoes
1 Cut leaf
2 Expose leaf to bacteria carrying an antigen gene and an antibiotic-resistance gene. Allow bacteria to deliver the genes into leaf cells
3 Expose leaf to an antibiotic to kill cells that lack the new genes. Wait for surviving (gene-altered) cells to multiply and form a clump (callus)
4 Allow callus to sprout shoots and roots
5 Put in soil. Within three months, the plantlets will grow into plants bearing antigen-laden vaccine potatoes

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played a good systemic response. Whether edible vaccines actually can protect against human disease remains to be determined, however.

Still to Be Accomplished

IN SHORT, the studies completed so far in animals and people have provided a proof of principle; they indicate that the strategy is feasible. Yet many issues must still be addressed. For one, the amount of vaccine made by a plant is low. Production can be increased in different ways—for instance, by linking antigen genes with regulatory elements known to help switch on the genes more readily or by engineering chloroplasts to manufacture more vaccine. As researchers solve that challenge, they will also have to ensure that any given amount of a vaccine food provides a predictable dose of antigen.

Additionally, workers could try to enhance the odds that antigens will activate the immune system instead of passing out of the body unused. General stimulators (adjuvants) and better targeting to the immune system might compensate in part for low antigen production.

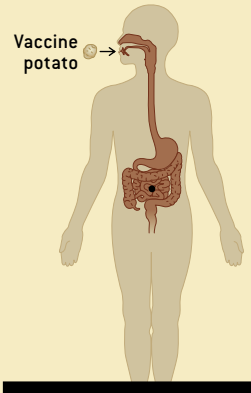
One targeting strategy involves linking antigens to molecules that bind well to immune system components known as M cells in the intestinal lining. M cells take in samples of materials that have entered the small intestine (including pathogens) and pass them to other cells of the immune system, such as antigen-presenting cells. Macrophages and other antigen-presenting cells chop up their acquisitions and display the resulting protein fragments on the cell surface. If white blood cells called helper T lymphocytes recognize the fragments as foreign, they may induce B lymphocytes (B cells) to secrete neutralizing antibodies and may also help initiate a broader attack on the perceived enemy.

It turns out that an innocuous segment of the *V. cholerae* toxin—the B subunit—binds readily to a molecule on M cells that ushers foreign material into those cells. By fusing antigens from other pathogens to this subunit, it should be possible to improve the uptake of antigens by M cells and to enhance immune responses to the added antigens. The B subunit also tends to associate with copies of itself, forming a doughnut-shaped, five-membered ring with a hole in the middle. These features raise the prospect of producing a multicomponent vaccine that brings several different antigens to M cells at once—thus potentially fulfulling an urgent need for a single vaccine that can protect against multiple diseases simultaneously.

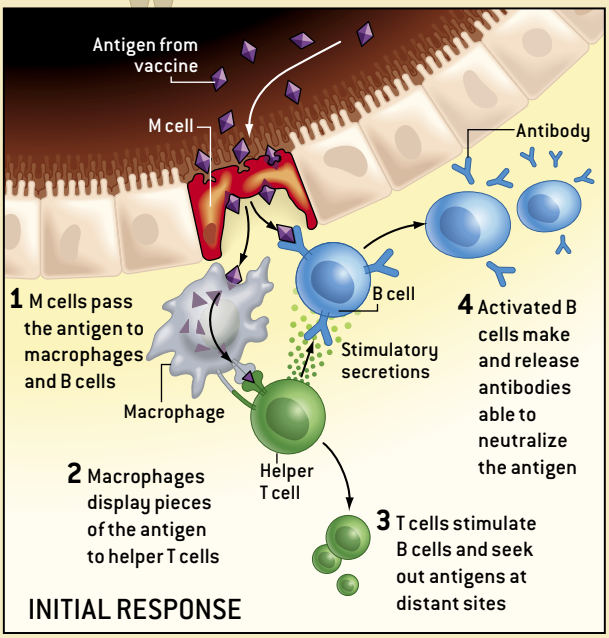
Researchers are also grappling with the reality that plants sometimes grow poorly when they start producing large amounts of a foreign protein. One solution would be to equip plants with regulatory elements that cause antigen genes to turn on—that is, give rise to the encoded antigens—only at selected times (such as after a plant is nearly fully grown or is exposed to some outside activator molecule) or only in its edible regions. This work is progressing.

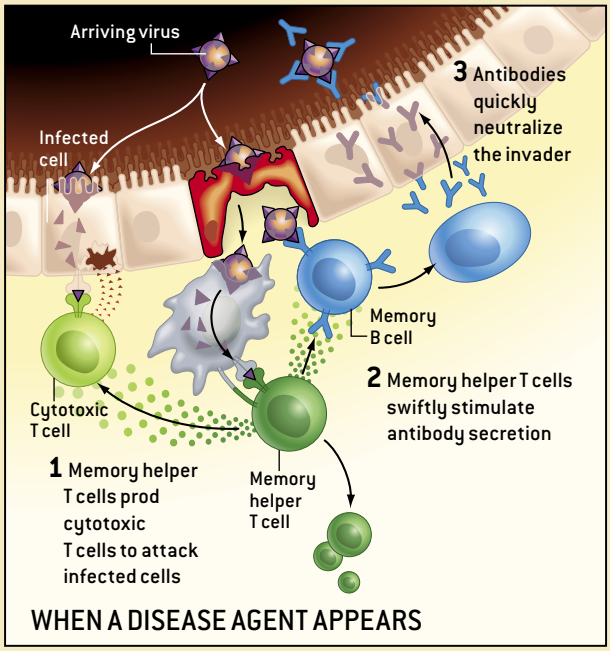
Further, each type of plant poses its own challenges. Potatoes are ideal in many ways because they can be propa-

HOW EDIBLE VACCINES PROTECT



An antigen in a food vaccine gets taken up by M cells in the intestine (*below, top*) and passed to various immune system cells, which then launch a defensive attack—as if the antigen were a true infectious agent, not just part of one. That response leaves long-lasting "memory" cells able to promptly neutralize the real infectious agent if it attempts an invasion (*bottom*).


Antigen from vaccine
M cell
Antibody
B cell
1 M cells pass the antigen to macrophages and B cells
Stimulatory secretions
4 Activated B cells make and release antibodies able to neutralize the antigen
Macrophage
Helper T cell
2 Macrophages display pieces of the antigen to helper T cells
3 T cells stimulate B cells and seek out antigens at distant sites
INITIAL RESPONSE


Arriving virus
3 Antibodies quickly neutralize the invader
Infected cell
Memory B cell
2 Memory helper T cells swiftly stimulate antibody secretion
Cytotoxic T cell
1 Memory helper T cells prod cytotoxic T cells to attack infected cells
Memory helper T cell
WHEN A DISEASE AGENT APPEARS

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In theory, a mother could eat a banana or two and thus trigger production of antibodies that would travel to her infant via breast milk.

gated from "eyes" and can be stored for long periods without refrigeration. But potatoes usually have to be cooked to be palatable, and heating can denature proteins. Indeed, as is true of tobacco plants, potatoes were not initially intended to be used as vaccine vehicles; they were studied because they were easy to manipulate. Surprisingly, though, many species of potatoes are actually eaten raw in South America. Also, contrary to expectations, cooking of potatoes does not always destroy the full complement of antigen. So potatoes may have more practical merit than most of us expected.

Bananas need no cooking and are grown widely in developing nations, but banana trees take a few years to mature, and the fruit spoils fairly rapidly after ripening. Tomatoes grow more quickly and are cultivated broadly, but they, too, may rot readily. Inexpensive methods of preserving these foods—such as freeze-drying—might overcome the spoilage problem. Among the other foods under consideration are lettuce, carrots, peanuts, rice, wheat, corn and soybeans.

In another concern, scientists need to be sure that vaccines meant to enhance immune responses do not backfire and suppress immunity instead. Research into a phenomenon called oral tolerance has shown that ingesting certain proteins can at times cause the body to shut down its responses to those proteins. To determine safe, effective doses and feeding schedules for edible vaccines, manufacturers will need to gain a better handle on the manipulations that influence whether an orally delivered antigen will stimulate or depress immunity.

A final issue worth studying is whether food vaccines ingested by mothers can indirectly vaccinate their babies. In theory, a mother could eat a banana or two and thus trigger production of antibodies that would travel to her fetus via the placenta or to her infant via breast milk. We have shown that this strategy is effective for protecting against rotavirus infection in mouse pups.

Nonscientific challenges accompany the technical ones. Not many pharmaceutical manufacturers are eager to support research for products targeted primarily to markets outside the lucrative West. International aid organizations and some national governments and philanthropies are striving to fill the gap, but the effort to develop edible vaccines remains underfunded.

In addition, edible vaccines fall under the increasingly unpopular rubric of "genetically modified" plants. A British company (Axis Genetics) that was supporting studies of edible vaccines failed; one of its leaders lays at least part of the blame on investor worry about companies involved with genetically engineered foods. I hope, however, that these vaccines will avoid serious controversy, because they are intended to save lives and would probably be planted over much less acreage than other food plants (if they are raised outside of greenhouses at all). Also, as drugs, they would be subjected to closer scrutiny by regulatory bodies.

Fighting Autoimmunity

CONSIDERATION of one of the challenges detailed here—the risk of inducing oral tolerance—has led my group and others to pursue edible vaccines as tools for quashing autoimmunity. Although oral delivery of antigens derived from infectious agents often stimulates the immune system, oral delivery of "autoantigens" (proteins derived from uninfected tissue in a treated individual) can suppress immune activity—a phenomenon seen frequently in test animals. No one fully understands the reasons for this difference.

Some of the evidence that ingesting autoantigens, or "self-antigens," might suppress autoimmunity comes from studies of type I diabetes, which results from autoimmune destruction of the insulin-producing cells (beta cells) of the pancreas. This destruction progresses silently for a time. Eventually, though, the loss of beta cells leads to a drastic shortage of insulin, a hormone needed to help cells take up sugar from the blood for energy. The loss results in high blood sugar levels. Insulin injections help to control diabetes, but they are by no means a cure; diabetics face an elevated risk of severe neurological and vascular complications.

In the past 20 years, investigators have identified several beta cell proteins that can elicit autoimmunity in people predisposed to type I diabetes. The main culprits, however, are insulin and a protein called GAD (glutamic acid decarboxylase). Researchers have also made progress in detecting when diabetes is "brewing." The next step, then, is to find ways of stopping the underground process before any symptoms arise.

THE AUTHOR

WILLIAM H. R. LANGRIDGE, a leader in the effort to develop edible vaccines for infectious and autoimmune diseases, is a professor in the department of biochemistry and at the Center for Health Disparities and Molecular Medicine at the Loma Linda University School of Medicine. After receiving his Ph.D. in biochemistry from the University of Massachusetts at Amherst in 1973, he conducted genetic research on insect viruses and plants at the Boyce Thompson Institute for Plant Research at Cornell University. In 1987 he moved to the Plant Biotechnology Center of the University of Alberta in Edmonton, and he joined Loma Linda in 1993.

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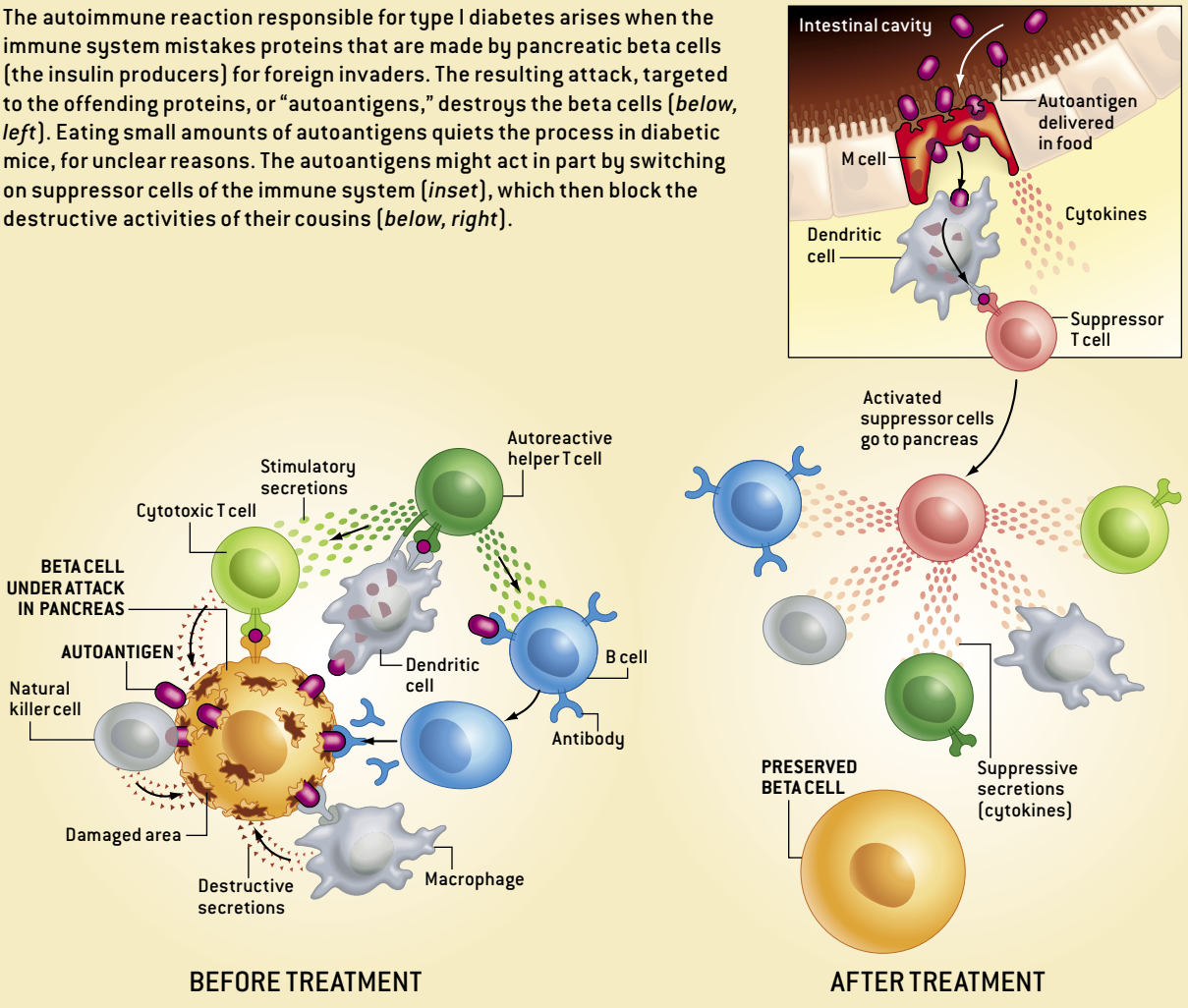
STOPPING AUTOIMMUNITY

The autoimmune reaction responsible for type I diabetes arises when the immune system mistakes proteins that are made by pancreatic beta cells (the insulin producers) for foreign invaders. The resulting attack, targeted to the offending proteins, or "autoantigens," destroys the beta cells (*below, left*). Eating small amounts of autoantigens quiets the process in diabetic mice, for unclear reasons. The autoantigens might act in part by switching on suppressor cells of the immune system (*inset*), which then block the destructive activities of their cousins (*below, right*).



To that end, my colleagues and I have developed plant-based diabetes vaccines, such as potatoes containing insulin or GAD linked to the nontoxic immunostimulating B subunit of the *V. cholerae* toxin (to enhance uptake of the antigens by M cells and processing by dendritic cells). Feeding of the vaccines to a mouse strain that becomes diabetic helped to suppress the immune attack and to prevent or delay the onset of high blood sugar.

Transgenic plants cannot yet produce the amounts of self-antigens that would be needed for a viable vaccine against human diabetes or other autoimmune diseases. But, as is true for infectious diseases, investigators are engineering chloroplasts to overcome this challenge.

Edible vaccines for combating autoimmunity and infectious diseases are close to being ready for large-scale testing in people. The technical obstacles seem surmountable. Nothing would be more satisfying than to protect the health of many millions of now defenseless children around the globe. SA

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MORE TO EXPLORE

Oral Immunization with a Recombinant Bacterial Antigen Produced in Transgenic Plants. Charles J. Arntzen in *Science,* Vol. 268, No. 5211, pages 714–716; May 5, 1995.

Immunogenicity in Humans of a Recombinant Bacterial Antigen Delivered in a Transgenic Potato. C. O. Tacket et al. in *Nature Medicine,* Vol. 4, No. 5, pages 607–609; May 1998.

A Plant-Based Cholera Toxin B Subunit-Insulin Fusion Protein Protects against the Development of Autoimmune Diabetes. Takeshi Arakawa, Jie Yu, D. K. Chong, John Hough, Paul C. Engen and William H. R. Langridge in *Nature Biotechnology,* Vol. 16, No. 10, pages 934–938; October 1998.

Plant-Based Vaccines for Protection against Infectious and Autoimmune Diseases. James E. Carter and William H. R. Langridge in *Critical Reviews in Plant Sciences,* Vol. 21, No.2, pages 93–109; March/April 2002.

Bacterial and Plant Enterotoxin B Subunit-Autoantigen Fusion Proteins Suppress Diabetes Insulitis. James E. Carter, Jie Yu, Nak-Won Choi, John Hough, David Henderson, Darren He and William H. R. Langridge in *Molecular Biotechnology,* Vol. 32, No. 1, pages 1–16; January 2006.

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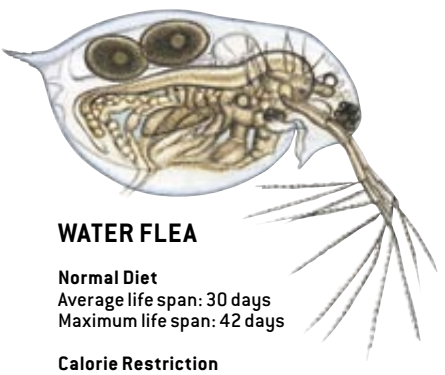
Calorie Restriction and Aging

By **Richard Weindruch**

Eating less—while maintaining adequate nutrition—is a recipe for longer life in many animals. Might it help humans as well?



WATER FLEA

Normal Diet
Average life span: 30 days
Maximum life span: 42 days

Calorie Restriction
Average life span: 51 days
Maximum life span: 60 days

WHITE RAT

Normal Diet
Average life span: 23 months
Maximum life span: 33 months

Calorie Restriction
Average life span: 33 months
Maximum life span: 47 months

SUZANNE BARNES

In 1935 scientists at Cornell University made an extraordinary discovery. By placing rats on a very low calorie diet, Clive M. McCay and his colleagues extended the outer limit of the animals' life span by 33 percent, from three years to four. They subsequently found that rats on low-calorie diets stayed youthful longer and suffered fewer late-life diseases than did their normally fed counterparts. Since the 1930s, calorie restriction has been the only intervention shown convincingly to slow aging in rodents (which are mammals, like us) and in creatures ranging from single-celled protozoans to roundworms, fruit flies and fish.

Naturally, the great power of the method raises the question of whether it can extend survival and good health in people. That issue is very much open, but the fact that the approach works in an array of organisms suggests the answer could well be yes. Some intriguing clues from monkeys and humans support the idea, too.

Of course, even if calorie austerity turns out to be a fountain of youth for humans, it might never catch on. After all, our track record for adhering to severe diets is poor. But scientists may one day develop drugs that will safely control our appetite over the long term or will mimic the beneficial influences of calorie control on the body's tissues. This last approach could enable people to consume fairly regular diets while still reaping the healthful effects of limiting their food intake. Many laboratories, including mine at the University of Wisconsin–Madison, are working to understand the cellular and molecular basis of how calorie restriction retards aging in animals. Our efforts may yield useful alternatives to strict dieting, although at the moment most of us are focused primarily on understanding the aging process (or processes) itself.

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HUMAN

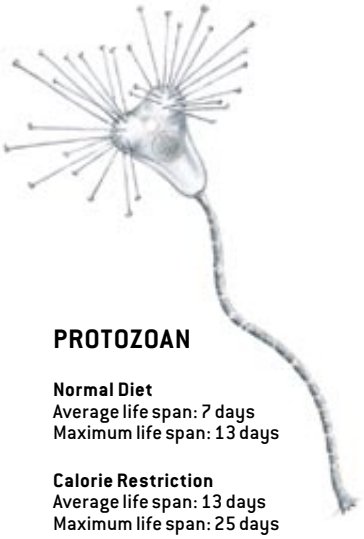
Normal Diet
Average life span: 75 years
Maximum life span: 110 years

Calorie Restriction
Average life span: ?
Maximum life span: ?

BOWL AND DOILY SPIDER

Normal Diet
Average life span: 50 days
Maximum life span: 100 days

Calorie Restriction
Average life span: 90 days
Maximum life span: 139 days



PROTOZOAN

Normal Diet
Average life span: 7 days
Maximum life span: 13 days

Calorie Restriction
Average life span: 13 days
Maximum life span: 25 days

Less Is More for Rodents

RESEARCH into calorie restriction has uncovered an astonishing range of benefits in animals—provided that the nutrient needs of the dieters are guarded carefully. In most studies the test animals, usually mice or rats, consume 30 to 50 percent fewer calories than are ingested by control subjects, and they weigh 30 to 50 percent less as well. At the same time, they receive enough protein, fat, vitamins and minerals to maintain efficient operation of their tissues. In other words, the animals follow an exaggerated form of a prudent diet, in which they consume minimal calories without becoming malnourished.

If the nutrient needs of the animals are protected, calorie restriction will consistently increase not only the average life span of a population but also the maximum life span—that is, the lifetime of the longest-surviving members of the group. This last outcome means that calorie restriction tinkers with some basic aging process. Anything that forestalls premature death, such as is caused by a preventable or treatable disease or by an accident, will increase the average life span of a population. But one must truly slow the rate of aging in order for the hardiest individuals to surpass the existing maximum.

Beyond altering survival, low-calorie diets in rodents have postponed most major diseases that are common late in life [*see box on page 57*], including cancers of the breast, prostate, immune system and gastrointestinal tract. Moreover, of the 300 or so measures of aging that have been studied, some 90 percent stay "younger" longer in calorie-restricted rodents than in well-fed ones. For example, certain immune responses decrease in normal mice at one year of age (middle age) but do not decline in slimmer but genetically identical mice until age two. Similarly, as rodents grow older they generally clear glucose, a simple sugar, from their blood less efficiently than they did in youth (a change that can progress to diabetes); they also synthesize needed proteins more slowly, undergo increased cross-linking (and thus stiffening) of long-lived proteins in tissues, lose muscle mass and learn less rapidly. In calorie-restricted animals, all these changes are delayed.

Not surprisingly, investigators have wondered whether calorie (energy) restriction per se is responsible for the advantages reaped from low-calorie diets or whether limiting fat or some other component of the diet accounts for the success. It turns out the first possibility is correct. Restriction of fat, protein or carbohydrate without calorie reduction does not increase the maximum life span of rodents. Supplementation alone with multivitamins or high doses of antioxidants does not work, and neither does variation in the type of dietary fat, carbohydrate or protein.

The studies also suggest, hearteningly, that calorie restriction can be useful even if it is not started until middle age. Indeed, the most exciting discovery of my career has been that calorie restriction initiated in mice at early middle age can extend the maximum life span by 10 to 20 percent and can oppose the development of can-

GUPPY

Normal Diet
Average life span: 33 months
Maximum life span: 54 months

Calorie Restriction
Average life span: 46 months
Maximum life span: 59 months

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cer. Further, although limiting the calorie intake to about half of that consumed by free-feeding animals increases the maximum life span the most, less severe restriction, whether begun early in life or later, also provides some benefit.

Naturally, scientists would be more confident that diet restriction could routinely postpone aging in men and women if the results in rodents could be confirmed in studies of monkeys (which more closely resemble people) or in members of our own species. To be most informative, such investigations would have to follow subjects for many years—an expensive and logistically difficult undertaking. Nevertheless, two major trials of monkeys are in progress.

THESE MICE ARE THE SAME AGE—40 months. Yet compared with the normally fed animal at the right, the one at the left, which has been reared on a low-calorie diet since 12 months of age (early middle age), looks younger and is healthier.

Lean, but Striking, Primate Data

IT IS TOO EARLY to tell whether low-calorie diets will prolong life or youthfulness in the monkeys over time. The projects have, however, been able to measure the effects of calorie restriction on so-called biomarkers of aging: attributes that generally change with age and may help predict the future span of health or life. For example, as primates grow older, their blood pressure and their blood levels of both insulin and glucose rise; at the same time, insulin sensitivity (the ability of cells to take up glucose in response to signals from insulin) declines. Postponement of these changes would imply that the experimental diet was probably slowing at least some aspects of aging.

One of the monkey studies, led by George S. Roth of the National Institute on Aging, began in 1987. It is examining rhesus monkeys, which typically live to about 27 years and sometimes reach 40 years, and squirrel monkeys, which rarely survive beyond 20 years. Some animals began diet restriction in youth (at one to two years), others after reaching puberty. The second project, involving only rhesus monkeys, was initiated in 1989 by William B. Ershler, Joseph W. Kemnitz and Ellen B. Roecker of the University of Wisconsin–Madison; I joined the team a year later. Our monkeys began calorie restriction as young adults, at eight to 14 years old. Both studies enforce a level of calorie restriction that is about 30 percent below the intake of normally fed control subjects.

So far the preliminary results are encouraging. The dieting animals in both projects seem healthy and happy, albeit eager for their meals, and their bodies seem to be responding to the regimen much as those of rodents do. Blood pressure and glucose levels are lower than in control animals, and insulin sensitivity is greater. The levels of insulin in the blood are lower as well.

No one has yet performed carefully controlled studies of long-term calorie restriction in average-weight humans over time. And data from populations forced by poverty to live on relatively few calories are uninformative, because such groups generally cannot attain adequate amounts of essential nutrients. Still, some human studies offer indirect evidence that calorie restriction could be of value. Consider the people of Okinawa, many of whom consume diets that are low in calories but provide needed nutrients. The incidence of centenarians there is high—up to 40 times greater than that of any other Japanese island. In addition, epidemiological surveys in the U.S. and elsewhere indicate that certain cancers, notably those of the breast, colon and stomach, occur less frequently in people reporting low calorie intakes.

Intriguing results were also obtained after eight people living in a self-contained environment—Biosphere 2, near Tucson, Ariz.—were forced to curtail their food intake sharply for two years because of poorer than expected yields from their food-producing efforts. The scientific merits of the overall project have been questioned, but those of us interested in the effects of low-calorie diets were fortunate that the late Roy L. Walford of the University of California, Los Angeles, who was an expert on calorie restriction and aging (and was my scientific mentor), was the team's physician. Walford helped his colleagues avoid malnutrition and monitored various aspects of the group's physiology. His analyses reveal that calorie restriction led to lowered blood pressure and glucose levels—just as it does in rodents and monkeys. Total serum cholesterol declined as well.

The results in monkeys and humans may be preliminary, but the rodent data show unequivocally that calorie restriction can exert a variety of beneficial effects. This variety raises something of a problem for researchers: Which of the many documented changes (if any) contributes most to increased longevity and youthfulness? Scientists have not yet reached a consensus, but they have ruled out a few once viable proposals. For instance, it is known that a low intake of energy retards growth and also shrinks the amount of fat in the body. Both these effects were once prime contenders as the main changes that lead to longevity but have now been discounted.

Several other hypotheses remain under consideration, however, and all of them have at least some experimental support. One such hypothesis holds that calorie restriction slows the rate of cell division in many tissues. Because the uncontrolled proliferation of cells is a hallmark of cancer, that change could potentially explain why the incidence of several late-life cancers is reduced in animals fed low-calorie diets. Another proposal is based on the finding that calorie

RICHARD WEINDRUCH

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restriction tends to lower glucose levels. Less glucose circulating in the blood would slow the accumulation of sugar on long-lived proteins and would thus moderate the disruptive effects of this buildup.

A Radical Explanation

THE VIEW that has so far garnered the most convincing support, though, holds that calorie restriction extends survival and vitality primarily by limiting injury of mitochondria by free radicals. Mitochondria are the tiny intracellular structures that serve as the power plants of cells. Free radicals are highly reactive molecules (usually derived from oxygen) that carry an unpaired electron at their surface. Molecules in this state are prone to destructively oxidizing, or snatching electrons from, any compound they encounter. Free radicals have been suspected of contributing to aging since the 1950s, when Denham Harman of the University of Nebraska Medical School suggested that their generation in the course of normal metabolism gradually disrupts cells. But it was not until the 1980s that scientists began to realize that mitochondria were probably the targets hit hardest.

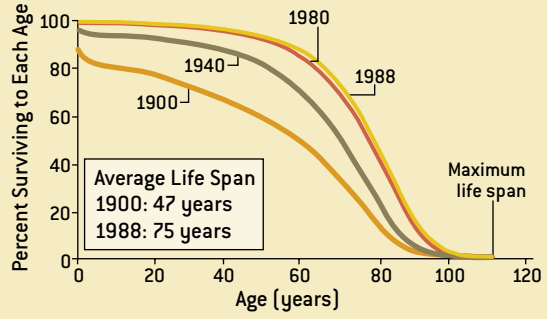
The mitochondrial free-radical hypothesis of aging derives in part from an understanding of how mitochondria produce ATP (adenosine triphosphate)—the molecule that provides the energy for most cellular processes, such as pumping ions across cell membranes, contracting muscle fibers and con-

Benefits of Calorie Restriction

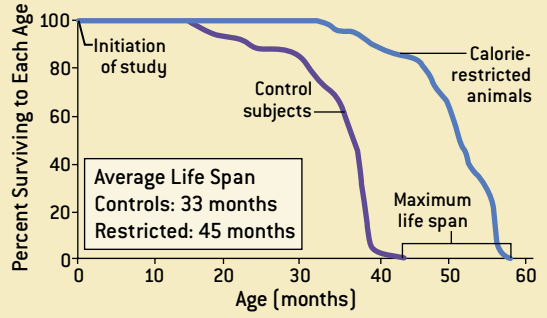
Since 1900, advances in health practices have greatly increased the average life span of Americans (*a*), mainly by improving prevention and treatment of diseases that end life prematurely. But those interventions have not substantially affected the maximum life span (*a*), which is thought to be determined by intrinsic aging processes. (The curves and the data in the inset show projections for people born in the years indicated and assume conditions influencing survival do not change.) Calorie restriction, in contrast, has markedly increased the maximum as well as the average life span in rodents (*b*) and is, in fact, the only intervention so far shown to slow aging in mammals—a sign that aging in humans might be retarded as well.

Although severe diets extend survival more than moderate ones, a study of mice fed a reduced-calorie diet from early in life (three weeks of age) demonstrates that even mild restriction offers some benefit (*c*). This finding is potentially good news for people. Also encouraging is the discovery that calorie restriction in rodents does more than prolong life; it enables animals to remain youthful longer (*table*). The calorie-restricted mouse at the left lived unusually long; most normally fed mice of her ilk die by 40 months. She was 53 months old when this photograph was taken and died of unknown causes about a month later.

a HUMAN SURVIVAL IN THE U.S.



b MOUSE SURVIVAL



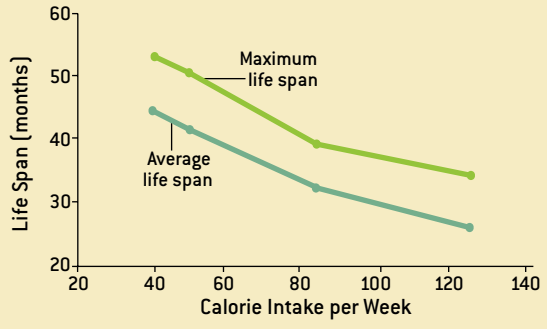
RESTRICTION IN RODENTS: SELECTED EFFECTS

POSTPONES AGE-RELATED DECLINES IN: Blood glucose control; female reproductive capacity; DNA repair; immunity; learning ability; muscle mass; protein synthesis

SLOWS AGE-RELATED INCREASES IN: Cross-linking of long-lived proteins; free-radical production by mitochondria; unrepaired oxidative damage to tissues

DELAYS ONSET OF LATE-LIFE DISEASES, INCLUDING: Autoimmune disorders; cancers; cataracts; diabetes; hypertension; kidney failure

c MOUSE SURVIVAL AT DIFFERENT LEVELS OF CALORIE INTAKE



LUCY READING-IKKANDA (*graphs*); RICHARD WEINDRUCH (*photograph*)

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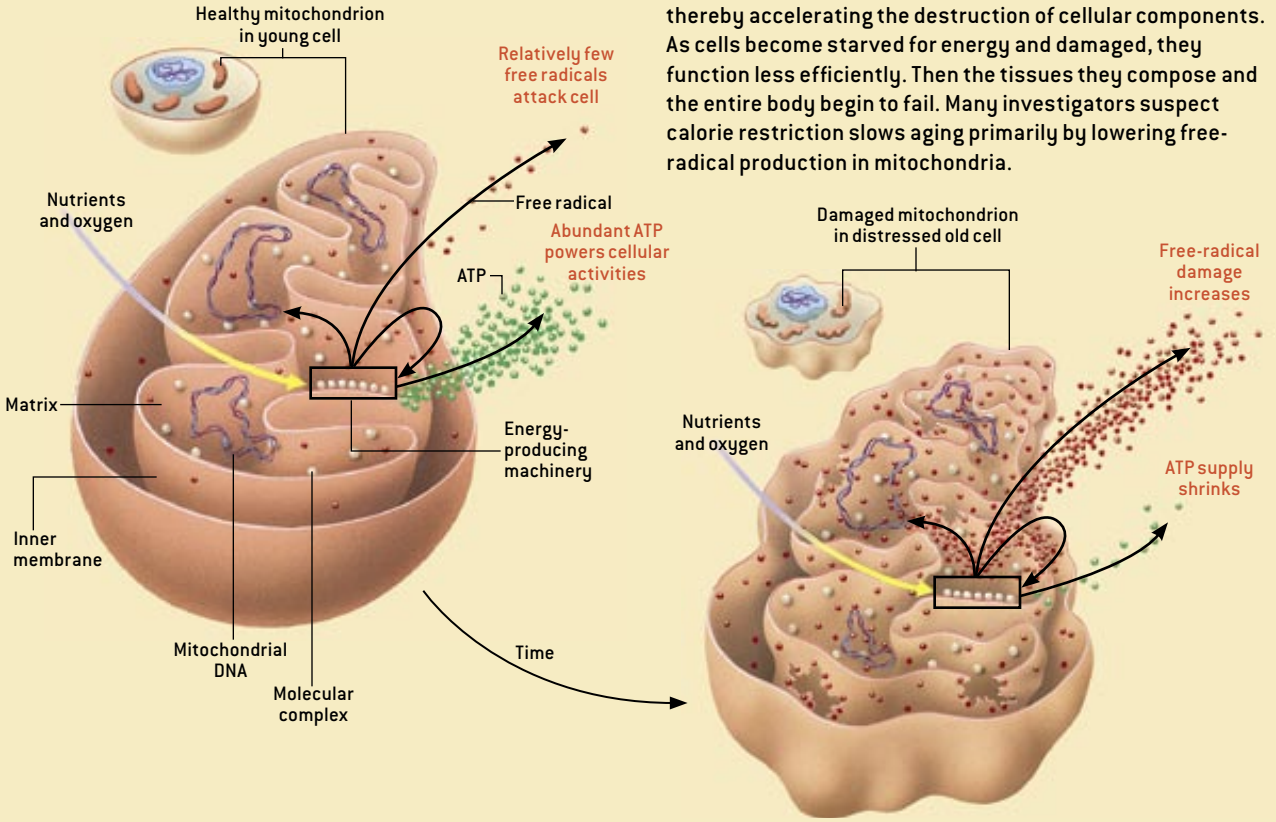
A THEORY OF AGING

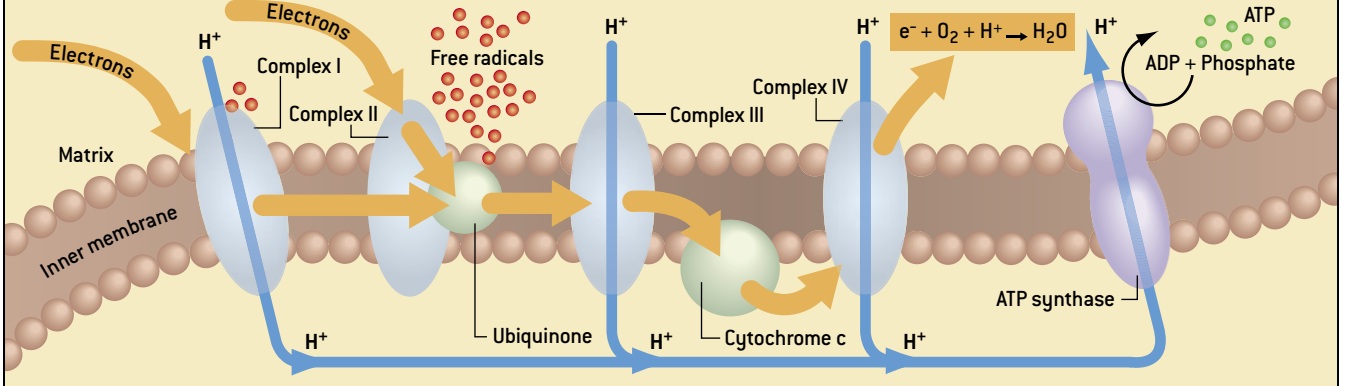
A leading explanation for why we age places much of the blame on destructive free radicals (*red*) generated in mitochondria, the cell's energy factories. The radicals form (*left*) when the energy-producing machinery in mitochondria (*boxed in black*) uses oxygen and nutrients to synthesize ATP (adenosine triphosphate)—the molecule (*green*) that powers most other activities in cells. Those radicals attack, and may permanently injure, the machinery itself and the mitochondrial DNA that is needed to construct parts of it. They can also harm other components of mitochondria and cells.

The theory suggests that over time (*right*) the accumulated damage to mitochondria precipitates a decline in ATP production. It also engenders increased production of free radicals, thereby accelerating the destruction of cellular components. As cells become starved for energy and damaged, they function less efficiently. Then the tissues they compose and the entire body begin to fail. Many investigators suspect calorie restriction slows aging primarily by lowering free-radical production in mitochondria.



THE MAKING OF ENERGY ... AND FREE RADICALS

The energy-producing machinery in mitochondria consists mainly of the electron-transport chain: a series of four large (*gray*) and two smaller (*light green*) molecular complexes. Complexes I and II (*far left*) take up electrons (*gold arrows*) from food and relay them to ubiquinone, the site of greatest free-radical (*red*) generation. Ubiquinone sends the electrons down the rest of the chain to complex IV, where they interact with oxygen and hydrogen to form water. The electron flow induces protons (H+) to stream (*blue arrows*) to yet another complex—ATP synthase (*purple*)—which draws on energy supplied by the protons to manufacture ATP (*dark green*). Free radicals form when electrons escape from the transport chain and combine with oxygen in their vicinity.



TOMO NARASHIMA (*top*); DANA BURNS-PIZER (*bottom*)

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structing proteins. ATP synthesis occurs by a very complicated sequence of reactions, but essentially it involves activity by a series of molecular complexes embedded in an internal membrane—the inner membrane—of mitochondria. With help from oxygen, the complexes extract energy from nutrients and use that energy to manufacture ATP.

Unfortunately, the mitochondrial machinery that draws energy from nutrients also produces free radicals as a by-product. Indeed, mitochondria are thought to be responsible for creating most of the free radicals in cells. One such by-product is the superoxide radical ($O_2^{\cdot -}$). (The dot in the formula represents the unpaired electron.) This renegade is destructive in its own right but can also be converted into hydrogen peroxide (H_2O_2), which technically is not a free radical but can readily form the extremely aggressive hydroxyl free radical ($OH^{\cdot -}$).

Once formed, free radicals can damage proteins, lipids (fats) and DNA anywhere in the cell. But the components of mitochondria—including the ATP-synthesizing machinery and the mitochondrial DNA that gives rise to some of that machinery—are believed to be most vulnerable. Presumably they are at risk in part because they reside at or near the "ground zero" site of free-radical generation and so are constantly bombarded by the oxidizing agents. Moreover, mitochondrial DNA lacks the protein shield that helps to protect nuclear DNA from destructive agents. Consistent with this view is that mitochondrial DNA suffers much more oxidative damage than does nuclear DNA drawn from the same tissue.

Proponents of the mitochondrial free-radical hypothesis of aging suggest that damage to mitochondria by free radicals eventually interferes with the efficiency of ATP production and increases the output of free radicals. The rise in free radicals, in turn, accelerates the oxidative injury of mitochondrial components, which inhibits ATP production even more. At the same time, free radicals attack cellular components outside the mitochondria, further impairing cell functioning. As cells become less efficient, so do the tissues and organs they compose, and the body itself becomes less able to cope with challenges to its stability. The body does try to counteract the noxious effects of the oxidizing agents. Cells possess antioxidant enzymes that detoxify free radicals, and they make other enzymes that repair oxidative damage. Neither of these systems is 100 percent effective, though, and so such injury is likely to accumulate over time.

Experimental Support

THE PROPOSAL that aging stems to a great extent from free-radical-induced damage to mitochondria and other cellular components has been buttressed by a number of findings. In one striking example, Rajindar S. Sohal of the University of Southern California, William C. Orr of Southern Methodist University and their colleagues investigated rodents and several other organisms, including fruit flies, houseflies, pigs and cows. They noted increases with age in free-radical generation by mitochondria and in oxidative changes to the inner mitochondrial membrane (where ATP is synthesized) and to mitochondrial proteins and DNA. They also observed that greater rates of free-radical production correlate with shortened average and maximum life spans in several of the species.

It turns out, too, that ATP manufacture decreases with age in the brain, heart and skeletal muscle, as would be expected if mitochondrial proteins and DNA in those tissues were irreparably impaired by free radicals. Similar decreases also occur in human tissues and may help explain why degenerative diseases of the nervous system and heart are common late in life and why muscles lose mass and weaken.

Some of the strongest support for the proposition that calorie restriction retards aging by slowing oxidative injury of mitochondria comes from Sohal's group. When the workers looked at mitochondria harvested from the brain, heart and kidney of mice, they discovered that the levels of the superoxide radical and of hydrogen peroxide were markedly lower in animals subjected to long-term calorie restriction than in normally fed controls. In addition, a significant increase of free-radical production with age seen in the control groups was blunted by calorie restriction in the experimental group. This blunted increase was, moreover, accompanied by lessened amounts of oxidative insult to mitochondrial proteins and DNA. Other work indicates that calorie restriction helps to prevent age-related changes in the activities of some antioxidant enzymes—although many investigators, including me, suspect that strict dieting ameliorates oxidative damage mainly through slowing free-radical production.

Applications to Humans?

BY WHAT MECHANISM might calorie restriction reduce the generation of free radicals? No one yet knows. One proposal holds that a lowered intake of calories may somehow lead to slower consumption of oxygen by mitochondria—either overall or in selected cell types. Alternatively, low-calorie diets may increase the efficiency with which mitochondria use oxygen, so that fewer free radicals are made per unit of oxygen consumed. Less use of oxygen or more efficient use would presumably result in the formation of fewer free radicals. Studies also intimate that calorie control may minimize free-radical generation in mitochondria by reducing levels of a circulating thyroid hormone known as triiodothyronine, or T_3, through unknown mechanisms.

Until research into primates has progressed further, few scientists would be prepared to recommend that large numbers of people embark on a severe calorie-restriction regimen.

THE AUTHOR

RICHARD WEINDRUCH, who earned his Ph.D. in experimental pathology at the University of California, Los Angeles, is professor of medicine at the University of Wisconsin–Madison and a researcher at the Veterans Administration Geriatric Research, Education and Clinical Center in Madison. He has devoted his career to the study of calorie restriction and its effects on the body and practices mild restriction himself. He has not, however, attempted to put his family, his dog or his two cats on the regimen.

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Nevertheless, the accumulated findings do offer some concrete lessons for those who wonder how such programs might be implemented in humans.

One implication is that sharp curtailment of food intake would probably be detrimental to children, considering that it retards growth in young rodents. Also, because children cannot tolerate starvation as well as adults can, they would presumably be more susceptible to any as yet unrecognized negative effects of a low-calorie diet (even though calorie restriction is not equivalent to starvation). An onset at about 20 years of age in humans should avoid such drawbacks and would probably provide the greatest extension of life.

The speed with which calories are reduced needs to be considered, too. Early researchers were unable to prolong survival of rats when diet control was instituted in adulthood. I suspect the failure arose because the animals were put on the regimen too suddenly or were given too few calories, or both. Working with year-old mice, my colleagues and I have found that a gradual tapering of calories to about 65 percent of normal did increase survival.

How might one determine the appropriate calorie intake for a human being? Extrapolating from rodents is difficult, but some findings imply that many people would do best by consuming an amount that enabled them to weigh 10 to 25 percent less than their personal set point. The set point is essentially the weight the body is "programmed" to maintain, if one does not eat in response to external cues, such as television commercials. The problem with this guideline is that determining an individual's set point is tricky. Instead of trying to identify their set point, dieters (with assistance from their health advisers) might engage in some trial and error to find the calorie level that reduces the blood glucose or cholesterol level, or some other measures of health, by a predetermined amount.

The research in animals further implies that a reasonable calorie-restriction regimen for humans might involve a daily intake of roughly one gram (0.04 ounce) of protein and no more than about half a gram of fat for each kilogram (2.2 pounds) of current body weight. The diet would also include enough complex carbohydrate (the long chains of sugars abundant in fruits and vegetables) to reach the desired level of calories. To attain the standard recommended daily allowances for all essential nutrients, an individual would have to select foods with extreme care and probably take vitamins or other supplements.

Anyone who contemplated following a calorie-restriction regimen would also have to consider potential disadvantages beyond hunger pangs and would certainly want to undertake the program with the guidance of a physician. Depending on the severity of the diet, the weight loss that inevitably results might impede fertility in females. Also, a prolonged anovulatory state, if accompanied by a diminution of estrogen production, might increase the risk of osteoporosis (bone loss) and loss of muscle mass later in life. It is also possible that calorie restriction would compromise a person's ability to withstand stress, such as injury, infection or exposure to extreme temperatures. Oddly enough, stress resistance has been little studied in rodents on low-calorie diets, and so they have little to teach about this issue.

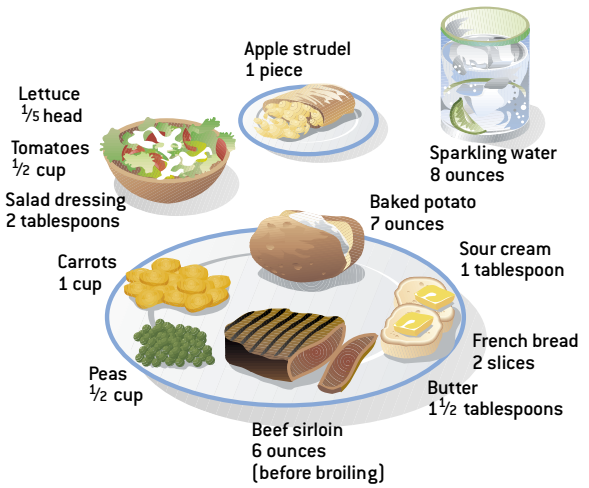
It may take another 10 or 20 years before scientists have a firm idea of whether calorie restriction can be as beneficial for humans as it clearly is for rats, mice and a variety of other creatures. Meanwhile investigators studying this inter-

Cutting Calories, Not Nutrients

Typical Meal

CALORIES: 1,268

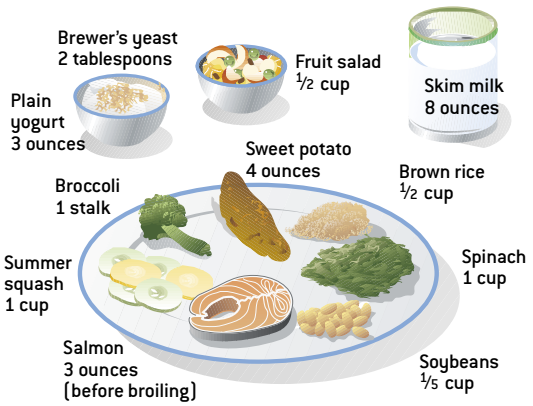
Percent from fat: 33; from protein: 22; from carbohydrate: 45



Calorie-Restricted Meal

CALORIES: 940

Percent from fat: 18; from protein: 32; from carbohydrate: 50



Dinner of a person on a roughly 2,000-calorie diet (*top*) might be reduced considerably—by about a third of the calories (*bottom*)—for someone on a calorie-restriction regimen. To avoid malnutrition, people on such programs would choose nutrient-dense foods such as those shown.

KARL GUDE; SOURCE: ROY L. WALFORD *University of California, Los Angeles*

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Signs of Slower Aging

Normal Diet

- FOOD INTAKE : 688 calories a day
- BODY WEIGHT: 31 pounds
- PERCENT OF WEIGHT FROM FAT: 25

MEASURES OF HEALTH

- Blood pressure: 129/60 (systole/diastole)
- Glucose level: 71 (milligrams per deciliter of blood)
- Insulin level: 93 (microunits per milliliter of blood)
- Triglycerides: 169 (milligrams per deciliter of blood)

Reduced Diet

- FOOD INTAKE : 477 calories a day
- BODY WEIGHT: 21 pounds
- PERCENT OF WEIGHT FROM FAT: 10

MEASURES OF HEALTH

- Blood pressure: 121/51 (systole/diastole)
- Glucose level: 56 (milligrams per deciliter of blood)
- Insulin level: 29 (microunits per milliliter of blood)
- Triglycerides: 67 (milligrams per deciliter of blood)

Results from an ongoing trial of calorie restriction in rhesus monkeys cannot yet reveal whether limiting calories will prolong survival. But comparison of a control group (*left*) with animals on a strict diet (*right*) after five years indicates that at least some biological measures that typically rise with age are changing more slowly in the test animals. Blood pressure is only slightly lower in the restricted group now but has been markedly lower for much of the study period.

vention are sure to learn much about the nature of aging and to gain ideas about how to slow it—whether through calorie restriction, through drugs that reproduce the effects of dieting or by methods awaiting discovery.

Postscript

SINCE PUBLICATION of this article a decade ago, the calorie-restriction (CR) field has become "hot," with great progress made on several fronts. One striking example is the use of short-lived "model organisms," such as yeasts, flies and worms, to rapidly obtain mechanistic insights into CR's effect on life span. The ease of genetic manipulation of these models has enabled the identification of key pathways and regulators of the response to CR. It is not surprising that most of these pathways involve aspects of energy metabolism. The core feature of CR is, after all, *energy* intake restriction.

New technology has also fueled rapid advances in the understanding of CR. The human genome comprises some 30,000 genes. Before 1998 one could evaluate the activity of only one gene at a time, by measuring the level of the messenger RNA molecule that it encodes. With the development of microarray technology, in a single experiment one can now evaluate the activities of thousands of genes. My colleagues and I were the first to implement the use of this technology in the context of aging and CR, by providing a global view of the activities of more than 6,000 genes in mouse muscle. Subsequently, this approach has been widely used in aging research.

The ultimate goal of the field is to understand the potential of CR in humans. Along the way, we hope to determine whether CR can slow the aging process in nonhuman primates, including species that share much of their genetic makeup with us. We have been comparing the effects of CR and a control diet on rhesus monkeys since 1989 and 1994 (two sets of studies were begun, with animals that were between eight and 14 years old at the outset). The monkeys on CR display signs of improved health and an emerging survival advantage compared with their age-matched controls. But the rhesus monkeys at our primate center have an average life span of about 27 years and a maximum life span of about 40 years, so it may be another 25 years before we obtain full survival data.

Progress has also been made on understanding the effects of long-term CR in humans. Direct evidence comes from studies of long-term practitioners of CR who display markedly improved risk-factor profiles for cardiovascular disease, including reductions in circulating insulin and glucose levels. These individuals also display fewer signs of deterioration in diastolic heart function. Additional progress in human CR is expected; the National Institute on Aging has funded three sites to conduct long-term CR investigations in humans.

The impressive accrual of knowledge on multiple aspects of CR can be expected to continue, and its pace to hasten, as increasing numbers of investigators focus on this fascinating intervention. The mechanistic understanding of calorie restriction will increase the likelihood of the development of drugs or nutrients that mimic the effects of CR in people consuming a normal diet. And if researchers can find a safe way to curb appetite, widespread practice of CR may become possible. Either way, calorie restriction appears well situated to contribute to aging retardation in humans. SA

MORE TO EXPLORE

The Retardation of Aging and Disease by Dietary Restriction. Richard Weindruch and Roy L. Walford. Charles C. Thomas, 1988.

Mitochondria, Oxidants, and Aging. Robert S. Balaban, Shino Nemoto and Toren Finkel in *Cell*, Vol. 120, No. 4, pages 483–495; February 25, 2005.

Toward a Unified Theory of Caloric Restriction and Longevity Regulation. David A. Sinclair in *Mechanisms of Ageing and Development*, Vol. 126, No. 9, pages 987–1002; September 2005.

KIRK BOEHM *Wisconsin Regional Primate Research Center (photographs)*

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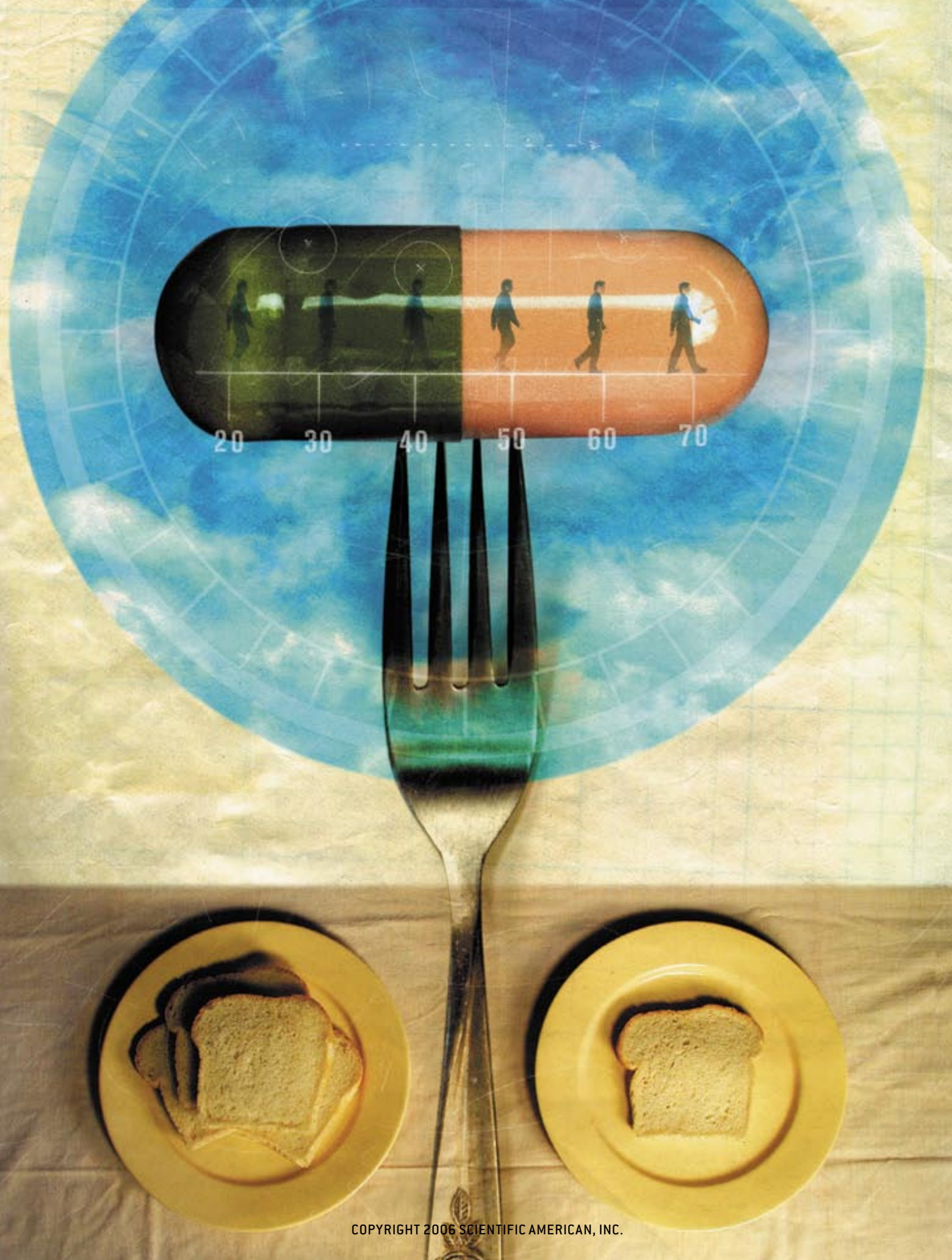

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The Serious Search for an Antiaging Pill

In government laboratories and elsewhere, scientists are seeking a drug able to prolong life and youthful vigor. Studies of calorie restriction are showing the way

By **Mark A. Lane, Donald K. Ingram** and **George S. Roth**

No treatment on the market has been proved to slow human aging—the buildup of molecular and cellular damage that increases vulnerability to infirmity as we grow older. But one intervention, consumption of a low-calorie yet nutritionally balanced diet, works incredibly well in a broad range of animals, increasing longevity and prolonging good health. Those findings suggest that calorie restriction could delay aging in humans, too.

Unfortunately, for maximum benefit, people would probably have to reduce their calorie intake by roughly 30 percent, equivalent to dropping from 2,500 calories a day to 1,750. Although a few hardy souls are currently attempting to do this, most mortals could not stick to that harsh a regimen, especially for years on end. But what if someone could create a pill that mimicked the physiological effects of eating less without actually forcing people to go hungry? Could such a calorie-restriction mimetic, as we call it, enable people to stay healthy longer, postponing age-related disorders (such as diabetes, atherosclerosis, heart disease and cancer) until very late in life?

We first posed this question in the mid-1990s, after we came upon a chemical agent that, in rodents, seemed to reproduce many of calorie restriction's benefits. Since then, we and others have been searching for a compound that would safely achieve the same feat in people. We have not succeeded yet, but our failures have been informative and have fanned hope that calorie-restriction, or CR, mimetics can indeed be developed eventually.

Our hunt for CR mimetics grew out of our desire to better understand calorie restriction's many effects on the body. Scientists first recognized the value of the practice more than 60 years ago, when they found that rats fed a low-calorie diet lived longer on average than free-feeding rats and had a reduced incidence of conditions that become increasingly common in old age. What is more, some of the treated animals survived longer than the oldest-living animals in the control group, which means that the maximum life span (the oldest attainable age), not merely the average life span, increased.

The rat findings have been replicated many times and extended to creatures ranging from yeast to fruit flies, worms, fish, spiders, mice and hamsters. Until fairly recently, the studies were limited to short-lived creatures genetically distant from humans. But a long-term study in dogs was published a couple of years ago to show that CR could be effective for our pets as well. A few long-term projects under way in a species more closely related to humans—the rhesus monkey—suggest that primates respond to calorie restriction almost identically to rodents, which makes us more optimistic than ever

STUART BRADFORD

CALORIE-RESTRICTION MIMETIC would, if successful, enable humans to derive many of the health and life-extending benefits seen in animals on restricted diets—without requiring people to go hungry.

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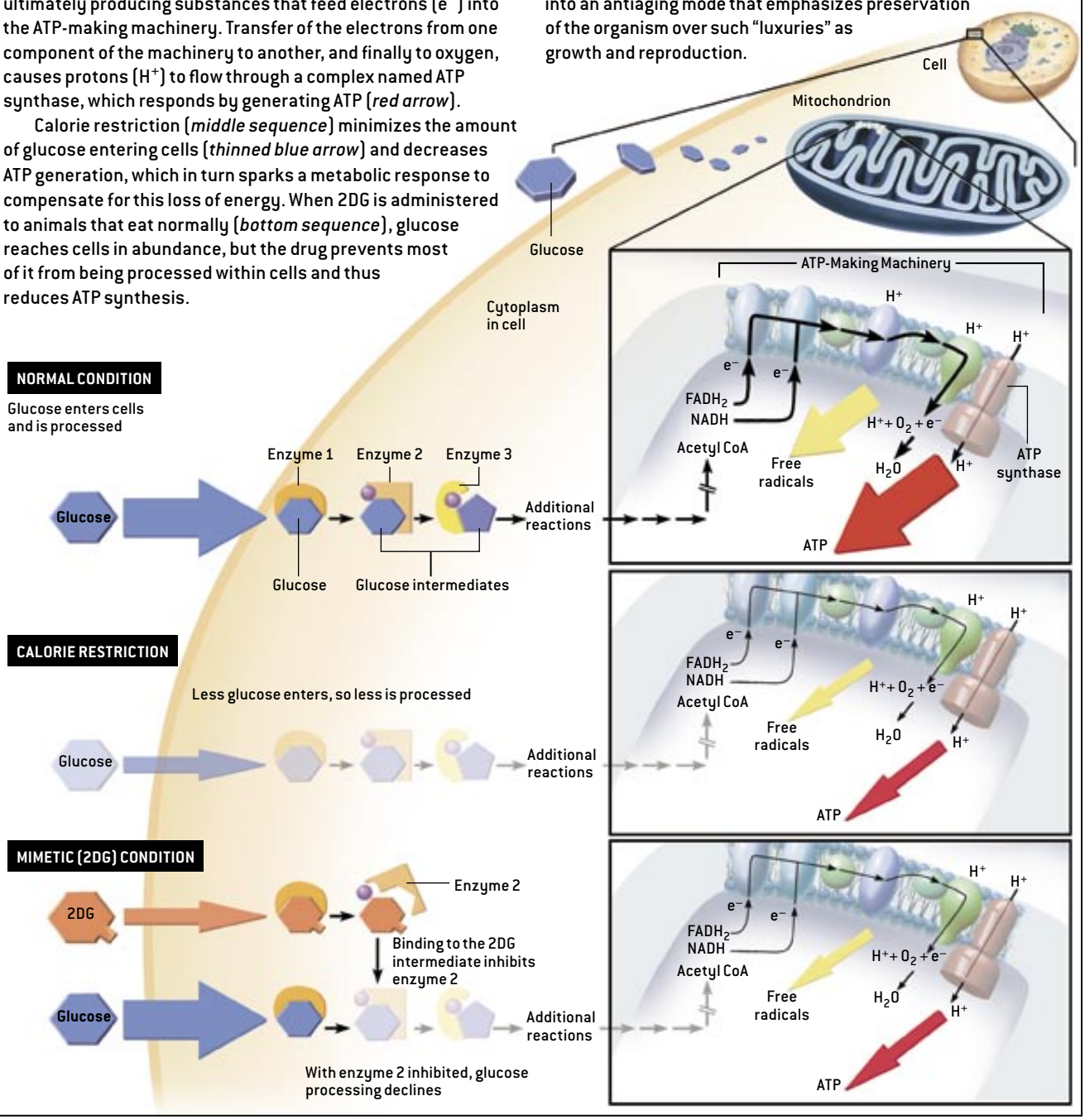
HOW A PROTOTYPE CALORIE-RESTRICTION MIMETIC WORKS

The best-studied candidate for a calorie-restriction mimetic, 2DG (2-deoxy-D-glucose), works by interfering with the way cells process the sugar glucose. It has proved toxic at some doses in animals and so cannot be used in humans. But it has demonstrated that chemicals can replicate the effects of calorie restriction; the trick is finding the right one.

Cells use the glucose from food to generate ATP (adenosine triphosphate), the molecule that powers many activities in the body (*top sequence*). More specifically, after glucose enters cells (*blue arrow*), a series of enzymatic reactions in the cytoplasm and mitochondria of cells alter the glucose bit by bit, ultimately producing substances that feed electrons (e^-) into the ATP-making machinery. Transfer of the electrons from one component of the machinery to another, and finally to oxygen, causes protons (H^+) to flow through a complex named ATP synthase, which responds by generating ATP (*red arrow*).

Calorie restriction (*middle sequence*) minimizes the amount of glucose entering cells (*thinned blue arrow*) and decreases ATP generation, which in turn sparks a metabolic response to compensate for this loss of energy. When 2DG is administered to animals that eat normally (*bottom sequence*), glucose reaches cells in abundance, but the drug prevents most of it from being processed within cells and thus reduces ATP synthesis.

Researchers have proposed several explanations for why interruption of glucose processing and ATP production might retard aging. One possibility relates to the ATP-making machinery's emission of free radicals (*yellow arrows*), which are thought to contribute to aging and to such age-related diseases as cancer by damaging cells. Reduced ATP induces a metabolic response to stimulate increased synthesis of mitochondria but also to improve their efficiency and thus limit the production of free radicals. Another hypothesis suggests that decreased processing of glucose produces a mild metabolic stress to indicate to cells that food is scarce (even if it is not) and induce them to shift into an antiaging mode that emphasizes preservation of the organism over such "luxuries" as growth and reproduction.



TERESE WINSLOW

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that CR mimetics could help people.

The monkey projects—initiated by our group at the National Institute on Aging in the late 1980s and by our colleagues at the University of Wisconsin–Madison in the early 1990s—demonstrate that, compared with control animals that eat normally, calorie-restricted monkeys have lower body temperatures and levels of the pancreatic hormone insulin, and as young adults they retain more youthful levels of certain hormones (such as DHEAS, or dehydroepiandrosterone sulfate) that tend to fall with age.

The animals also look better on indicators of risk for age-related diseases. For example, they have lower blood pressure and triglyceride levels (signifying a decreased likelihood of heart disease), and they have more normal blood glucose levels (pointing to a reduced risk for diabetes, which is marked by unusually high blood glucose levels). They and the other monkeys must be followed still longer, however, before we will know whether low food intake can increase both average and maximum life spans in monkeys: rhesus monkeys typically live about 25 years and sometimes up to 40. Findings in primates bode well for the possibility that CR will have beneficial effects in humans. Indeed, we have demonstrated that biological hallmarks of CR, such as decreased insulin and body temperature and a slowed rate of decline in serum DHEAS levels, are associated with better survival in men from the Baltimore Longitudinal Study of Aging.

The Journey Starts

BY 1995 WE WANTED to know how the many physiological and biochemical changes induced by calorie restriction actually delayed aging in mammals. We suspected that changes in cellular metabolism would be key. By "metabolism" we mean the uptake of nutrients from the blood and their conversion to energy usable for cellular activities. We focused on metabolism in part because the benefits of calorie restriction clearly depend on reducing the overall amount or temporal pattern of fuel coming into the body for processing. Also, calorie restriction affects aging in a wide variety of tissues, which implies that it alters biological processes present in all cells. Few processes are more fundamental than metabolism.

We specifically wondered whether changes related to metabolism of the sugar glucose would account for CR's benefits. Glucose, which forms when the body digests carbohydrates, is the primary source of energy in the body. We also wanted to know whether alterations in the secretion and activity of insulin, which influences glucose use by cells, would be important. Insulin is secreted as glucose levels in the blood rise after a meal, and it serves as the key that opens cell "doors" to the sugar. We concentrated on glucose and insulin because reductions in their levels and increases in cellular sensitivity to insulin are among the most consistent hallmarks of calorie restriction in both rodents and primates, occurring very soon after restriction is begun.

Others began publishing data showing that metabolic processes involving glucose and insulin influence life span. For instance, several investigations achieved remarkable extensions of life span in nematode worms by mutating genes similar to those involved in molecular responses to insulin in mammals. More recently, researchers have found that lowered intake of glucose or disruption of glucose processing can extend life span in yeast.

An "Aha!" Moment

AROUND THE TIME the nematode work came out, we began to scour the scientific literature for ways to manipulate insulin secretion and sensitivity without causing diabetes or its opposite, hypoglycemia. Our search turned up studies from the 1940s and 1950s mentioning a compound called 2-deoxy-D-glucose (2DG) that was being tested in rodents for treating cancer but that also reportedly lowered insulin levels in the blood. As we perused the literature further, we had a true "aha!" moment.

If 2DG could mimic calorie restriction in animals, perhaps it would do the same for people.

The compound apparently reproduced many classic responses to calorie restriction—among them reduced tumor growth, lowered temperature and elevated levels of glucocorticoid hormones. If 2DG really could mimic many aspects of calorie restriction in animals, we thought, perhaps it would do the same for people.

While we were planning our first studies of 2DG, we learned that 2DG worked by disrupting a key enzyme involved in processing glucose in cells. The compound structurally resembles glucose, so it enters cells readily. Initial metabolism of 2DG resembles that of glucose, but subsequent metabolism is inhibited such that glucose process-

THE AUTHORS

MARK A. LANE, DONALD K. INGRAM and *GEORGE S. ROTH* researched calorie restriction for many years at the National Institute on Aging of the National Institutes of Health. Lane is now director of project management at Wyeth in Collegeville, Pa., and continues to collaborate with Ingram and Roth. After 26 years at the NIA, Ingram retired as chief of the laboratory of experimental gerontology and is now professor and head of the Nutritional Neuroscience and Aging Laboratory at the Pennington Biomedical Research Center of the Louisiana State University System in Baton Rouge, where he continues to conduct research in CR mimetics. Roth, who spent nearly 30 years as a full-time researcher at the NIA, is now chief executive officer of GeroScience, a biotechnology venture devoted to antiaging strategies.

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Calorie Restriction's Varied Effects

Rodents and monkeys on calorie restriction differ from their more abundantly fed counterparts in many ways, some of which are listed below (*1–3*). Although the influence of these shared changes on aging remains to be clarified, the close similarities in the responses of rodents and monkeys encourage hope that the health-promoting and antiaging effects long seen in rodents (*1–4*) are universal among mammals, including humans. If so, calorie-restriction mimetics should help people live well longer. The effects marked by capsules (*below*) have been reproduced in rats by the compound 2DG.

1. **EFFECTS INDICATIVE OF ALTERED GROWTH, DEVELOPMENT OR METABOLISM**
   - Lower body temperature
   - Later sexual maturation
   - Later skeletal maturation

2. **EFFECTS INDICATIVE OF IMPROVED HEALTH**
   - Lower weight
   - Less abdominal fat

3. **EFFECTS INDICATIVE OF REDUCED RISK FOR AGE-RELATED DISEASES (SUCH AS DIABETES AND HEART DISEASE)**
   - Greater sensitivity to insulin
   - Lower fasting insulin level
   - Lower fasting glucose level
   - Lower cholesterol and triglyceride levels
   - Lower insulinlike growth factor 1 level
   - Higher levels of "good" (HDL) cholesterol
   - Slower decline in level of the hormone melatonin

4. **EFFECTS FOUND IN RODENTS BUT STILL UNDER INVESTIGATION IN MONKEYS**
   - Later onset of age-related diseases (including cancer)
   - More cell suicide (which may help limit tumor growth)
   - Longer average life span
   - Longer maximum life span (a strong sign of slowed aging)

ing essentially chokes on the intermediate compound produced from 2DG [*see box on page 64*].

The net result is that cells make smaller amounts of glucose's by-products, just as occurs when calorie restriction limits the amount of glucose going into cells. In essence, 2DG tricks the cell into a metabolic state similar to that seen during calorie restriction, even though the body is taking in normal amounts of food. The "metabolic stress" produced by CR or a CR mimetic forces the cellular machinery to work harder to restore ATP to required levels. Studies have shown that the mitochondria actually proliferate in response to this demand and also operate more efficiently while producing fewer dangerous by-products of metabolism.

Why might more efficient functioning of the ATP-producing machinery help combat aging? We cannot say with certainty, but we have some ideas. A long-standing theory of aging blames the production of molecules called free radicals. The lion's share of free radicals in the body are emitted as the ATP-making machinery operates. Over time these highly reactive molecules are thought to cause permanent damage to various parts of cells, including the protein complexes that generate ATP. Thus, the metabolic stress produced in the cell by 2DG and calorie restriction slow the rate at which free radicals form and disrupt cells. 2DG may alter metabolism in another way by limiting insulin secretion and thereby minimizing insulin's unwanted actions in the body.

We also suspect that cells interpret reduced levels of raw materials for the ATP-making machinery as a signal that food supplies are scarce. Cells may well respond to that message by switching to a self-protective mode, inhibiting activities not needed for cell maintenance and repair—such as reproduction—and pouring most of their energy into preserving the integrity of their parts. If that idea is correct, it could explain why calorie restriction has been shown to increase production of substances that protect cells from excess heat and other stresses.

This adoption of a self-preservation mode would mirror changes that have been proposed to occur on an organismic level in times of food scarcity. In the generally accepted "disposable soma" theory of aging, Thomas Kirkwood of Newcastle University in England has proposed that organisms balance the need to procreate against the need to maintain the body, or soma. When resources are plentiful, organisms can afford both to maintain themselves and to grow and reproduce. But when food is limited, the body invokes processes that inhibit growth and reproduction and takes extra care to preserve the soma.

Recent research has indicated another potential pathway for mimicking CR. A National Institute on Aging study led by R. Michael Anson showed that a regimen of intermittent fasting—in which mice were allowed free access to food on alternating days—resulted in beneficial effects similar to those of calorie restriction, including reduced blood glucose and insulin levels and increased resistance of brain cells to toxic stress. Surprisingly, the food intake and body weight of these mice did not diverge substantially from control mice that had unlimited access to food. These data suggest that an absolute reduction in calorie intake may not underlie all of CR's effects; rather hormonal changes related to the stress of intermittent fasting may

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play an important role. CR and 2DG both induce this mild stress, as indicated by higher circulating levels of the stress hormone corticosterone. Many investigators now think that this mild stress conditions the organism to better withstand even more extreme stress.

Testing Begins

IN OUR FIRST experiments on 2DG's effectiveness, we delivered low doses to rats by adding it to their feed for six months. The treatment moderately reduced fasting blood glucose levels, body weight and temperature and robustly reduced fasting insulin levels—findings consistent with the actions of calorie restriction itself. Interestingly, after an initial adjustment to the novel diet, the 2DG group did not eat significantly less food than the controls. Thus, these exciting preliminary analyses revealed that it was possible to mimic at least some sequelae of calorie restriction without reducing food intake.

Shortly after we published these results, in 1998, other groups began identifying more ways that 2DG imitates calorie restriction, including reduced heart rate and increased resistance to stress and toxins. Subsequently we initiated a long-term study of rats on a diet supplemented with 2DG. The results confirmed our previous findings that 2DG slightly reduces blood glucose and body temperature. Contrary to our expectations, however, the 2DG diet in this experiment did not extend maximum life span. Animals treated with 2DG showed better survival for the first half of the life span, but maximum life span was not extended, because of cardiac toxicity.

The work so far clearly provides a "proof of concept" that inhibiting glucose metabolism can re-create many effects of calorie restriction. Regrettably, 2DG has a fatal flaw preventing it from being a "magic pill." Though safe at certain low levels, it apparently becomes toxic for some animals when the amount delivered is raised just a bit or given over long periods. The narrowness of the safety zone separating helpful and toxic doses would bar it from human use. We hope this is not a general feature of CR mimetics.

Moving On

ASSUMING OUR long-term studies confirm that inhibiting metabolism can retard aging, the task becomes finding other substances that yield 2DG's benefits but are safer over a broader range of doses and delivery schedules. Several candidates seem promising in early studies, including iodoacetate, which inhibits cellular metabolism, as 2DG does, but through a different mechanism. Treatment with antidiabetic medications that enhance cellular sensitivity to insulin might be helpful as well, as long as the amounts given do not cause blood glucose levels to fall too low. Metformin (Glucophage), which has resulted in moderate life-span extension in preliminary animal experiments, has been suggested as a possible candidate in this category.

A great deal of research implicates glucose metabolism in regulating life span, yet other aspects of metabolism can also change in reaction to calorie restriction. When the body cannot extract enough energy from glucose in food, it may shift to breaking down protein and fat. Pharmaceuticals that target these processes might serve as CR mimetics, either alone or in combination with drugs that intervene in glucose metabolism. Some compounds that act in those pathways have already been identified, although researchers have not yet assessed their potential as CR mimetics.

Drugs that replicate only selected effects of calorie restriction could have a role to play as well. In theory, antioxidant vitamins might fit that bill. Research conducted to date, however, indicates that this particular intervention probably will not extend longevity. Resveratrol, an antioxidant found in grapes and red wine, affects certain genes (the sirtuins) that may be involved in CR, at least in lower animal models. Lipoic acid, another antioxidant, is currently being used in combination with acetylcarnitine, a metabolic efficiency enhancer, to produce some antiaging effects. In fact, this "cocktail" is now commercially available. Several companies, including GeroScience, are pursuing various CR mimetic strategies.

Unlike the multitude of elixirs being touted as the latest antiaging cure, CR mimetics would alter fundamental processes that underlie aging. Many candidate mimetics, such as resveratrol, appear to work "downstream" in the sequence of events that elicit the antiaging effects of CR, although glycolytic inhibitors such as 2DG come closest to targeting the "causes," rather than the "symptoms" or pathologies, of aging.

To illustrate this important point, consider that average life span has increased from about 40 years in the early 1900s to about 80 years today while maximum life span has remained unchanged at about 122 years. Much, if not all, of the increase in average life span has resulted from improved health care and nutrition. Thus, to truly "mimic" CR and alter the fundamental biology of aging, candidate compounds must be shown to increase both maximum and average life span. The goal is to devise compounds that fool cells into activating maintenance and repair activities that lead to greater health and longevity of the organism. If scientists can develop agents that offer the benefits of 2DG without its drawbacks, they will finally enable people to have their cake—a longer, healthier life—and eat it, too. SA

MORE TO EXPLORE

2-Deoxy-D-Glucose Feeding in Rats Mimics Physiological Effects of Caloric Restriction. Mark A. Lane, George S. Roth and Donald K. Ingram in *Journal of Anti-Aging Medicine,* Vol. 1, No. 4, pages 327–337; Winter 1998.

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Unlocking the Secrets of Longevity Genes

A handful of genes that control the body's defenses during hard times can also dramatically improve health and prolong life in diverse organisms. Understanding how they work may reveal the keys to extending human life span while banishing diseases of old age

By **David A. Sinclair** and **Lenny Guarente**

TAPPING THE POWER of longevity genes could change the arc of a typical human lifetime: instead of vitality and growth giving way to the decline of old age, a person might be able to retain the youthfulness he feels at 50 when he is 70, 90 or well past 100.

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You can assume quite a bit about the state of a used car just from its mileage and model year. The wear and tear of heavy driving and the passage of time will have taken an inevitable toll. The same appears to be true of aging in people, but the analogy is flawed because of a crucial difference between inanimate machines and living creatures: deterioration is not inexorable in biological systems, which can respond to their environments and use their own energy to defend and repair themselves.

At one time, scientists believed aging to be not just deterioration but an active continuation of an organism's genetically programmed development. Once an individual achieved maturity, "aging genes" began to direct its progress toward the grave. This idea has been discredited, and conventional wisdom now holds that aging really is just wearing out over time because the body's normal maintenance and repair mechanisms simply wane. Evolutionary natural selection, the logic goes, has no reason to keep them working once an organism has passed its reproductive age.

Yet we and other researchers have found that a family of genes involved in an organism's ability to withstand a stressful environment—such as excessive heat or scarcity of food or water—have the power to keep its natural defense and repair activities going strong regardless of age. By optimizing the body's functioning for survival, these genes maximize the individual's chances of getting through the crisis. And if they remain activated long enough, they can also dramatically enhance the organism's health and extend its life span. In essence, they represent the opposite of aging genes—longevity genes.

We began investigating this idea nearly 15 years ago by imagining that evolution would have favored a universal regulatory system to coordinate this well-known response to environmental stress. If we could identify the gene or genes that serve as its master controllers and thereby act as master regulators of an organism's life span, these natural defense mechanisms might be turned into weapons against the diseases and decline that are now apparently synonymous with human aging.

Many recently discovered genes, known by such cryptic names as *daf-2*, *pit-1*, *aak-2*, *clk-1* and *p66Shc*, have been found to affect stress resistance and life span in laboratory organisms, suggesting that they could be part of a fundamental mechanism for surviving adversity [*see box on page 72*]. Our own two laboratories have focused on a gene called *SIR2*, variants of which are present in all organisms studied so far, from yeast to humans. Extra copies of the gene increase longevity in creatures as diverse as yeast, roundworms and fruit flies, and we are working to determine whether *SIR2* does the same for larger animals, such as mice.

As one of the first longevity genes to have been identified, *SIR2* is the best characterized, so we will focus here

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on its workings. They illustrate how a genetically regulated survival mechanism can extend life and improve health, and growing evidence suggests that *SIR2* may be *the* key regulator of that mechanism.

Silence Is Golden

WE FIRST DISCOVERED that *SIR2* is a longevity gene by asking what causes individual baker's yeast cells to grow old and whether a single gene might control aging in this simple organism. The notion that an understanding of yeast life span would tell us anything about human aging was deemed preposterous by many. Aging in yeast is measured by counting how many times mother cells divide to produce daughters before dying. A typical yeast cell's life span is about 20 divisions.

One of us (Guarente) began by screening yeast colonies for unusually long-lived cells in the hope of finding genes responsible for their longevity. This screen yielded a single mutation in a gene called *SIR4*, which encodes part of a complex of proteins containing the Sir2 enzyme. The mutation in *SIR4* caused the Sir2 protein to gather at the most highly repetitive region of the yeast genome, a stretch containing the genes that encode the protein factories of the cell, known as ribosomal DNA (rDNA). More than 100 of these rDNA repeats exist in the average yeast cell's genome, and they are difficult to maintain in a stable state. Repetitive sequences are prone to "recombining" with one another, a process that in humans can lead to numerous illnesses, such as cancer and Huntington's disease. Our yeast findings suggested that aging in mother cells was caused by some form of rDNA instability that was mitigated by the Sir proteins.

In fact, we found a surprising kind of rDNA instability. After dividing several times, yeast mother cells spin off extra copies of the rDNA as circular rings that pop out of the genome. These extrachromosomal rDNA circles (ERCs) are copied along with the mother cell's chromosomes prior to cell division but remain in the mother cell's nucleus afterward. Thus, a mother cell accumulates an ever increasing number of circles that eventually spell her doom, possibly because copying the ERCs consumes so many resources that she can no longer manage to replicate her own genome.

When an extra copy of the *SIR2* gene was added to the yeast cell, however, formation of the rDNA circles was repressed and the cell's life span was extended by 30 percent. That finding explained how *SIR2* could act as a longevity gene in yeast, but amazingly, extra copies of the *SIR2* gene also extended the life span of roundworms by as much as 50 percent. We were surprised not only by this commonality in organisms separated by a vast evolutionary distance but by the fact that the adult worm body contains only nondividing cells—thus, the replicative aging mechanism in yeast could not apply to worms. We wanted to know exactly what the *SIR2* gene does.

As we soon discovered, the gene encodes an enzyme with a completely novel activity. Cellular DNA is wrapped around a complex of packaging proteins called histones. These bear chemical tags, such as acetyl groups, that determine how snugly the histones package DNA. Removing acetyl groups from histones tightens the packaging further and renders the DNA inaccessible to the enzymes responsible for popping the rDNA circles out of the chromosome. This deacetylated form of DNA is said to be silent because any genes in these regions of the genome are rendered inaccessible to being activated.

Sir proteins were already known to be involved in gene silencing—indeed, SIR stands for silent information regulator. Sir2 is one of several enzymes that remove acetyl tags from the histones, but we found that it is unique in that its enzymatic activity absolutely requires a ubiquitous small molecule called NAD, which has long been known as a conduit of many metabolic reactions in cells. This association between Sir2 and NAD was exciting because it linked Sir2 activity to metabolism and thus potentially to the relation between diet and aging observed in calorie restriction.

The Calorie Connection

RESTRICTING AN ANIMAL'S calorie intake is the most famous intervention known to extend life span. Discovered more than 70 years ago, it is still the only one absolutely proved to work. The restricted regime typically involves reducing an individual's food consumption by 30 to 40 percent compared with what is considered normal for its species. Animals ranging from rats and mice to dogs and possibly primates that remain on this diet not only live longer but are far healthier during their prolonged lives. Most diseases, including cancer, diabetes and even neurodegenerative illnesses, are forestalled. The organism seems to be supercharged for survival. The only apparent trade-off in some creatures is a loss of fertility.

Understanding the mechanisms by which calorie restriction works and developing medicines that reproduce its health benefits have been tantalizing goals for decades. The phenomenon was long attributed to a simple slowing down of metabolism—cells' produc-

OVERVIEW

LIFTING LIMITS ON LIFE SPAN

- Genes that control an organism's ability to withstand adversity cause changes throughout the body that render it temporarily supercharged for survival.
- Activated over the long term, this stress response prolongs life span and forestalls disease in a wide range of organisms.
- Sirtuins are a family of genes that may be master regulators of this survival mechanism.
- Understanding how they produce their health- and longevity-enhancing effects could lead to disease treatments and ultimately longer, disease-free human life spans.

PRECEDING PAGES: CARY WOLINSKY (*photographs*); JEN CHRISTIANSEN (*photocomposition*)

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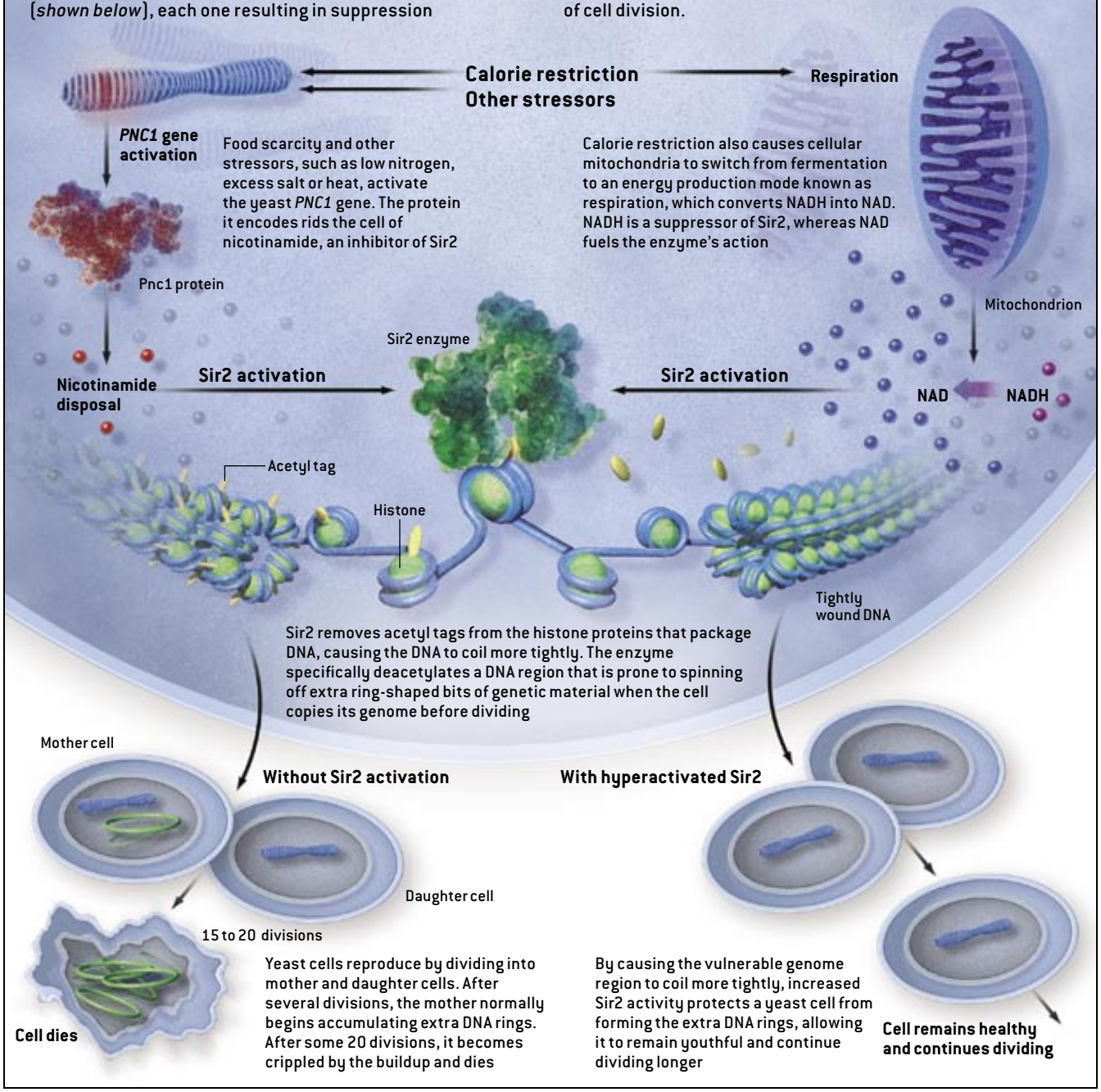
tion of energy from fuel molecules—and therefore reduction of its toxic byproducts in response to less food.

But this view now appears to be incorrect. Calorie restriction does not slow metabolism in mammals, and in yeast and worms, metabolism is both sped up and altered by the diet. We believe, therefore, that calorie restriction is a biological stressor like natural food scarcity that induces a defensive response to boost the organism's chances of survival. In mammals, its effects include changes in cellular defenses, repair, energy production and activation of programmed cell death known as apoptosis. We were eager to know what part Sir2 might play in such changes, so we looked first at its role during calorie restriction in simple organisms.

In yeast, we have found that re-

SIR2 AND STRESS IN YEAST

Moderate stress extends the life span of yeast about 30 percent by stimulating increased activity of the Sir2 enzyme. Stressors can boost Sir2 activity via two distinct pathways (*shown below*), each one resulting in suppression of a Sir2 inhibitor. The hyperactivated Sir2, in turn, represses a form of genome instability that normally would contribute to the yeast cell's death after about 20 cycles of cell division.


Calorie restriction
Other stressors
Respiration
PNC1 gene activation
Food scarcity and other stressors, such as low nitrogen, excess salt or heat, activate the yeast *PNC1* gene. The protein it encodes rids the cell of nicotinamide, an inhibitor of Sir2
Calorie restriction also causes cellular mitochondria to switch from fermentation to an energy production mode known as respiration, which converts NADH into NAD. NADH is a suppressor of Sir2, whereas NAD fuels the enzyme's action
Pnc1 protein
Mitochondrion
Sir2 enzyme
Nicotinamide disposal
Sir2 activation
Sir2 activation
NAD
NADH
Acetyl tag
Histone
Tightly wound DNA
Sir2 removes acetyl tags from the histone proteins that package DNA, causing the DNA to coil more tightly. The enzyme specifically deacetylates a DNA region that is prone to spinning off extra ring-shaped bits of genetic material when the cell copies its genome before dividing
Mother cell
Without Sir2 activation
With hyperactivated Sir2
Daughter cell
15 to 20 divisions
Yeast cells reproduce by dividing into mother and daughter cells. After several divisions, the mother normally begins accumulating extra DNA rings. After some 20 divisions, it becomes crippled by the buildup and dies
By causing the vulnerable genome region to coil more tightly, increased Sir2 activity protects a yeast cell from forming the extra DNA rings, allowing it to remain youthful and continue dividing longer
Cell dies
Cell remains healthy and continues dividing

TAMI TOLPA

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stricting food availability affects two pathways that increase Sir2 enzymatic activity in the cells. On one hand, calorie restriction turns on a gene called *PNC1*, which produces an enzyme that rids cells of nicotinamide, a small molecule similar to vitamin B_3 that normally represses Sir2. Consistent with the idea that calorie restriction is a stressor that activates a survival response, *PNC1* is also stimulated by other mild stressors known to extend yeast life span, such as increased temperature or excessive amounts of salt.

A second pathway induced in yeast by restricted calories is respiration, a mode of energy production that creates NAD as a by-product while lowering levels of its counterpart, NADH. It turns out that not only does NAD activate Sir2, but NADH is an inhibitor of the enzyme, so altering the cell's NAD/NADH ratio profoundly influences Sir2 activity.

Having seen how life-extending biological stress increases Sir2 activity, the question became, Is Sir2 necessary to produce the longevity? The answer appears to be a resounding yes. One way to test whether Sir2 is essential to this process is to remove its gene and determine whether the effect remains. In organisms as complex as fruit flies, calorie restriction does require *SIR2* to extend life span. And because the body of an adult fruit fly contains numerous tissues that are analogous to mammalian organs, we suspect that calorie restriction in mammals is also likely to require *SIR2*.

Yet if humans are ever to reap the health benefits of calorie restriction,

Genetic Pathways That Extend Life Span

Scientists studying longevity have identified an assortment of genes that can influence life span in different organisms. Like *SIR2* and its gene relatives (the sirtuins), some of them promote longer life when more copies of the gene are present or activity by the protein it encodes is increased. Many of the genes and their proteins have a negative effect on life span, however, so reducing their activity enhances longevity.

In worms, for example, the gene that encodes cellular receptors for insulin and insulinlike growth factor 1 (IGF-1) is called *daf-2*. Suppressing the *daf-2* gene's activity in adult worms interferes with signaling via insulin and IGF-1 and extends the organisms' lives by as much as 100 percent. Suppressing several other growth-related genes or intervening in the pathways of molecular activity they trigger has also been found to promote longevity.

Several of the genes listed below (or their proteins) have been shown to regulate or be regulated by sirtuins during calorie restriction, suggesting that they could be part of a master regulatory network for aging. The authors speculate that *SIR2* and its relatives may orchestrate this network.

GENE OR PATHWAY (HUMAN EQUIVALENT)	ORGANISM/LIFE SPAN EXTENSION	MORE OR LESS IS BETTER	MAJOR PROCESSES INFLUENCED	POSSIBLE SIDE EFFECTS OF MANIPULATION
SIR2 (*SIRT1*)	Yeast, worm, fly/ 30 percent	More	Cell survival, metabolism and stress responses	None known
TOR (*TOR*)	Yeast, worm, fly/ 30 to 250 percent	Less	Cell growth and nutrient sensing	Increased infections, cancer
Daf/FoxO proteins (Insulin, IGF-1)	Worm, fly, mouse/ 100 percent	Less	Growth and glucose metabolism	Dwarfism, sterility, cognitive decline, tissue degeneration
Clock (*CoQ*)	Worm/30 percent	Less	Co-enzyme Q synthesis	None known
aak-2 (*AMPK*)	Worm/10 percent	More	Metabolism and stress responses	None known
Growth hormone (Growth hormone)	Mouse, rat/ 7 to 150 percent	Less	Body size regulation	Dwarfism
p66Shc (*p66Shc*)	Mouse/27 percent	Less	Free-radical production	None known
Catalase (*CAT*)	Mouse/15 percent	More	Detoxification of hydrogen peroxide	None known
Prop1, pit1 (*Pou1F1*)	Mouse/42 percent	Less	Pituitary activity	Dwarfism, sterility, hypothyroidism
Klotho (*Klotho*)	Mouse/ 18 to 31 percent	More	Insulin, IGF-1 and vitamin D regulation	Insulin resistance
Methuselah (*CD97*)	Fly/35 percent	Less	Stress resistance and nerve cell communication	None known

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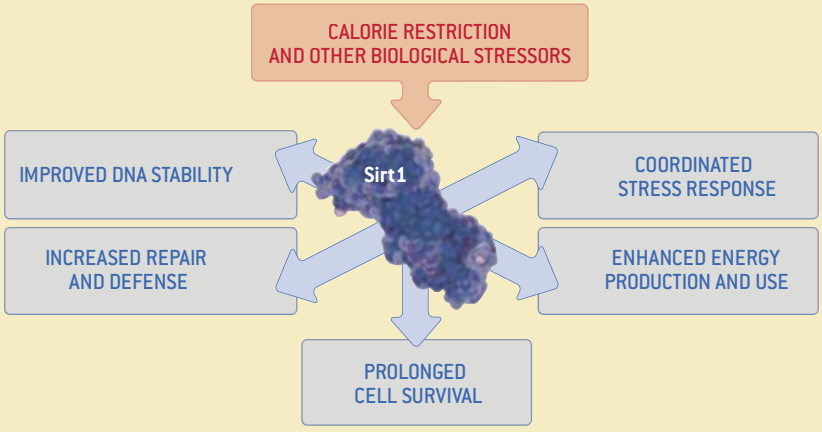
Orchestrator of Beneficial Change



SIRT1 ENZYME appears to be responsible for the health- and longevity-enhancing effects of calorie restriction in mammals. Food scarcity and other biological stressors trigger increased activity by Sirt1, which in turn alters activities within cells. By boosting manufacture of certain signaling molecules, such as insulin, Sirt1 may also coordinate the stress response throughout the body. The enzyme produces its effects by modifying other proteins [*see box on next page*].

radical dieting is not a reasonable option. Drugs that can modulate the activity of Sir2 and its siblings (collectively referred to as sirtuins) in a similar manner will be needed. Just such a sirtuin-activating compound, or STAC, called resveratrol has proved particularly interesting. Resveratrol is a small molecule present in red wine and manufactured by a variety of plants when they are stressed. At least 18 other compounds produced by plants in response to stress have also been found to modulate sirtuins, suggesting that the plants may use such molecules to control their own Sir2 enzymes.

Feeding resveratrol to yeast, worms or flies or placing them on a calorie-restricted diet extends their life spans about 30 percent, but only if they possess the *SIR2* gene. Moreover, a fly that overproduces Sir2 has an increased life span that cannot be further extended by resveratrol or calorie restriction. The simplest interpretation is that calorie restriction and resveratrol each prolong the lives of fruit flies by activating Sir2.

Resveratrol-fed flies not only live longer, despite eating as much as they want, but they do not suffer from the reduced fertility often caused by calorie restriction. This is welcome news for those of us hoping to treat human diseases with molecules that target Sir2 enzymes. But first we want a better understanding of the role of Sir2 in mammals.

Leader of the Band

THE MAMMALIAN VERSION of the yeast *SIR2* gene is known as *SIRT1* ("*SIR2* homolog 1"). It encodes a protein, Sirt1, that has the same enzymatic activity as Sir2 but that also deacetylates a wider variety of proteins both inside the cell nucleus and out in the cellular cytoplasm. A few of these proteins targeted by Sirt1 have been identified and are known to control critical processes, including apoptosis, cell defenses and metabolism. The potential longevity-enhancing role of the *SIR2* gene family seems, therefore, to be preserved in mammals. But not surprisingly in larger and more complex organisms, the pathways by which sirtuins achieve their effect have grown considerably more complicated as well.

Increased Sirt1 in mice and rats, for example, allows some of the animals' cells to survive in the face of stress that would normally trigger their programmed suicide. Sirt1 does this by regulating the activity of several other key cellular proteins, such as p53, FoxO and Ku70, that are involved either in setting a threshold for apoptosis or in prompting cell repair. Sirt1 thus enhances cellular repair mechanisms while buying time for them to work.

Over the course of a lifetime, cell loss from apoptosis may be an important factor in aging, particularly in nonrenewable tissues such as the heart and brain, and slowing cell death may be one way sirtuins promote health and longevity. A striking example of Sirt1's ability to foster survival in mammalian cells can be seen in the Wallerian mutant strain of mouse. In these mice, a single gene is duplicated, and the mutation renders their neurons highly resistant to stress, which protects them against stroke, chemotherapy-induced toxicity and neurodegenerative diseases.

In 2004 Jeffrey D. Milbrandt of Washington University in St. Louis and his colleagues showed that the Wallerian gene mutation in these mice increases the activity of an enzyme that makes NAD, and the additional NAD appears to protect the neurons by activating Sirt1. Moreover, Milbrandt's group found that STACs such as resveratrol conferred a protective effect on the neurons of normal mice similar to the Wallerian mutation.

In a more recent study by Christian Néri of the French National Institute of Health and Medical Research, resveratrol and another STAC, fisetin, were shown to prevent nerve cells from dying in two different animal models (worm and mouse) of human Huntington's disease. In both cases, the protection by STACs required sirtuin gene activity.

The protective effect of sirtuins in individual cells is becoming increasingly clear. But if these genes are the mediators of calorie restriction's benefits, an unsolved puzzle remains how diet can regulate their activities and thus the rate of aging in an entire animal. Recent research by Pere Puigserver of the Johns Hopkins University School of Medicine and his colleagues has shown that NAD levels rise in liver cells under fasting conditions, prompting in-

TAMI TOLPA [*illustration*]; LUCY READING-IKKANDA [*diagram*]

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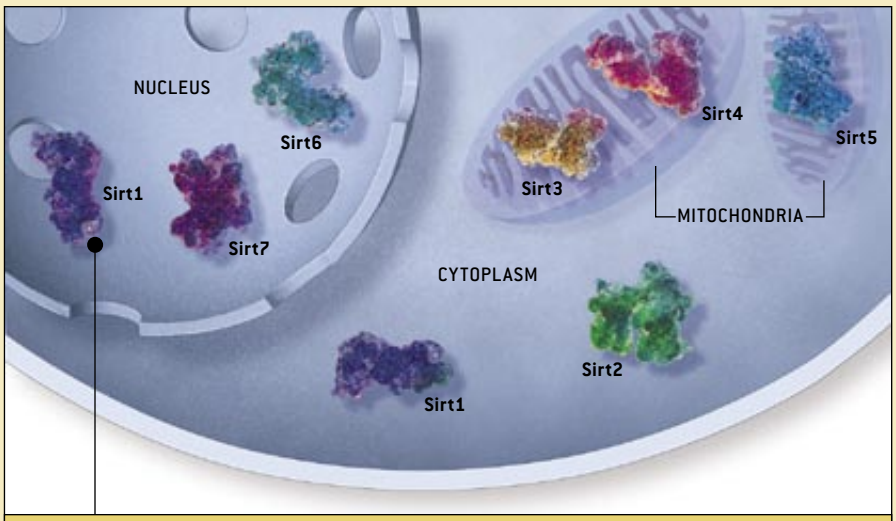
SIRTUINS IN THE CELL

The Sirt1 enzyme is the best characterized sirtuin, but it is not the only one found in mammals. Genes related to *SIRT1* give rise to similar enzymes that act in various locations within cells. Sirt1 operates both in the nucleus and in the cytoplasm, deacetylating other proteins and thereby altering their behavior. Many of its targets are transcription factors that directly activate genes or are regulators of those factors [*see examples below right*].

Scientists are just beginning to identify the roles of the other sirtuins and to determine whether they, too, influence longevity. Sirt2 is known to modify tubulin, a component of a cell's internal scaffolding, and may affect cell division. Sirt3 is active in the cell's energy generators, the mitochondria, and appears to participate in regulating body temperature. Sirt4 is a mitochondrial sirtuin that modulates metabolic adaptation to calorie restriction. The function of Sirt5 is unknown. Mutations in the gene encoding Sirt6 have been associated with premature aging. Sirt7 controls the production of "ribosomal RNAs" required for the production of proteins.



SOME PROTEIN TARGETS OF SIRT1

FoxO1, FoxO3 and FoxO4: Transcription factors for genes involved in cell defenses and glucose metabolism

Histones H3, H4 and H1: Control DNA packing in chromosomes

Ku70: Factor that promotes DNA repair and cell survival

MyoD: Transcription factor that promotes muscle development and tissue repair

NCoR: Regulator that affects multiple genes, including those involved in fat metabolism, inflammation and the functioning of other regulators, such as PGC-1α

NF-κB: Transcription factor that controls inflammation, cell survival and cell growth

P300: Regulator that causes acetyl tags to be added to histones

P53: Transcription factor that triggers programmed cell death in damaged cells

PGC-1α: Regulator that controls cellular respiration and plays a central role in muscle development

creased Sirt1 activity. Among the proteins Sirt1 acts on is an important regulator of gene transcription called PGC-1α, which then causes changes in the cell's glucose metabolism. Thus, Sirt1 was found to act as both a sensor of nutrient availability and a regulator of the liver's response.

Similar data have given rise to the idea that Sirt1 is a central metabolic regulator in liver, muscle and fat cells because it senses dietary variations via changes in the NAD/NADH ratio within cells and then exerts far-reaching effects on the pattern of gene transcription in those tissues. This model would explain how Sirt1 may integrate many of the genes and pathways that affect longevity described on page 72.

More than one mechanism may mediate Sirt1's bodywide activities, however. Another appealing hypothesis is that mammals register their food availability by the amount of energy they have stored in the form of body fat. Fat cells secrete hormones that convey signals to the other tissues in the body, but their message depends on the levels of fat stored. By reducing fat stores, calorie restriction may establish a pattern of hormone signals that communicates "scarcity," which activates cell defenses. Consistent with this idea is the fact that mice genetically engineered to be extra lean regardless of their food intake tend to live longer.

This possibility led us to wonder whether Sirt1, in turn, also regulates fat storage in response to diet. Indeed, Sirt1 activity is increased in fat cells after food limitation, causing fat stores to move from the cells into the blood-

TAMI TOLPA

THE AUTHORS

DAVID A. SINCLAIR and *LENNY GUARENTE* began working together to identify longevity-regulating genes and unravel their mechanisms in 1995, when Sinclair became a postdoctoral fellow in Guarente's lab at the Massachusetts Institute of Technology. Sinclair is now director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard Medical School and an associate of the Broad Institute in Cambridge, Mass. Guarente, Novartis Professor of Biology, has been on the faculty of M.I.T. for 25 years. His lab first identified the *SIR2* gene as the controller of life span in yeast and showed that the enzyme it encodes is responsible for the beneficial effects of calorie restriction in that organism. Today both authors are investigating the mammalian version of the gene, *SIRT1*. Sinclair's company Sirtris and Guarente's firm Elixir are each developing sirtuin-activating molecules for pharmaceutical use.

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stream for conversion to energy in other tissues. We surmise that Sirt1 senses the diet, then dictates the level of fat storage and thus the pattern of hormones produced by fat cells. This effect on fat and the signals it sends would, in turn, set the pace of aging in the entire organism and make Sirt1 a key regulator of the longevity conferred by calorie restriction in mammals. It would also closely link aging and metabolic diseases, including type 2 diabetes, associated with excess fat. Intervening pharmacologically in the Sirt1 pathway in fat cells might therefore forestall not only aging but also specific ailments.

Another critical process modified by Sirt1 is inflammation, which is involved in a number of disorders, including cancer, arthritis, asthma, heart disease and neurodegeneration. Recent work by Martin W. Mayo and his colleagues at the University of Virginia has shown that Sirt1 inhibits NF-κB, a protein complex that promotes the inflammatory response. The Sirt1-activating compound resveratrol has the same effect. This finding is particularly encouraging, both because the search for molecules that inhibit NF-κB is a highly active area of drug development and because another well-known effect of calorie restriction is its ability to suppress excessive inflammation.

If *SIR2* is thus the master controller of a regulatory system for aging that is activated by stress, it may function by acting as the conductor of an orchestra of players that includes hormonal networks, intracellular regulatory proteins and other genes associated with longevity. One might ask whether the mammalian sirtuins other than Sirt1 are involved in calorie restriction. The answer appears to be yes. Under energy limitation, organisms catabolize fats and amino acids rather than store them. Sirt4 is a mitochondrially residing sirtuin that plays an important role in regulating this dietary adaptation. Sirt4 determines whether the amino acids glutamate and glutamine are processed for energy by regulating the enzyme glutamate dehydrogenase inside mitochondria. We suspect that most or all of the seven sirtuins direct metabolic changes in mammals that contribute to the stress resistance and longevity conferred by a calorie-restricted diet.

From Defense to Advance

BECAUSE PEOPLE have sought to slow aging for tens of thousands of years without success, some may find it hard to accept that human aging might be controlled by tweaking a handful of genes. Yet we know it is possible to forestall aging in mammals with a simple dietary change: calorie restriction works. And we have shown that sirtuin genes control many of the same molecular pathways as calorie restriction. Without actually knowing the precise, and potentially myriad, causes of aging, we have already demonstrated in a variety of lifeforms that it can be delayed by manipulating a few regulators and letting them take care of the organisms' health.

We also know that the *SIR2* family of genes evolved far back in time because today they are found in organisms ranging from baker's yeast, *Leishmania* parasites and roundworms to flies and humans. In all these organisms but the last, which has not yet been tested, sirtuins dictate length of life. This fact alone convinces us that human sirtuin genes probably hold the key to our health and longevity as well.

Both our labs are running carefully controlled mouse experiments that should soon tell us whether the *SIRT1* gene controls health and life span in a mammal. We may not know definitively how sirtuin genes affect human longevity for decades. Those who are hoping to pop a pill and live to 130 may have therefore been born a bit too early. Nevertheless, those of us already alive could live to see medications that modulate the activity of sirtuin enzymes employed to treat specific conditions such as Alzheimer's, cancer, diabetes and heart disease. In fact, several such drugs have begun clinical trials for treatment of diabetes, herpes and neurodegenerative diseases.

And in the longer term, we expect that unlocking the secrets of longevity genes will allow society to go beyond treating illnesses associated with aging and prevent them from arising in the first place. It may seem hard to imagine what life will be like when people are able to feel youthful and live relatively free of today's diseases well into their 90s. Some may wonder whether tinkering with human life span is even a good idea. But at the beginning of the 20th century, life expectancy at birth was around 45 years. It has risen to about 75 thanks to the advent of antibiotics and public health measures that allow people to survive or avoid infectious diseases. Society adapted to that dramatic change in average longevity, and few people would want to return to life without those advances. No doubt, future generations accustomed to living past 100 will also look back at our current approaches to improving health as primitive relics of a bygone era. SA

Without actually knowing the precise causes of aging, we have demonstrated that it can be delayed.

MORE TO EXPLORE

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Obesity: An Overblown Epidemic?

Dissenting researchers accuse government and medical authorities—as well as the media—of misleading the public about the health consequences of rising body weights

By **W. Wayt Gibbs**

Could it be that excess fat is not, by itself, a serious health risk for the vast majority of people who are overweight or obese—categories that in the U.S. include about six of every 10 adults? Is it possible that urging the overweight or mildly obese to cut calories and lose weight may actually do more harm than good?

Such notions defy conventional wisdom that excess adiposity kills more than 300,000 Americans a year and that the gradual fattening of nations since the 1980s presages coming epidemics of diabetes, cardiovascular disease, cancer and a host of other medical consequences. Indeed, just this past August a large study of retirees published in the *New England Journal of Medicine* by scientists at the National Cancer Institute (NCI) and the National Institutes of Health concluded that "excess body weight during midlife, including overweight, is associated with an increased risk of death." And in March 2005 that journal presented a "Special Report" by S. Jay Olshansky, David B. Allison and others who asserted that because of the obesity epidemic, "the steady rise in life expectancy during the past two centuries may soon come to an end." Articles about the special report by the *New York Times*, the *Washington Post* and many other news outlets emphasized its forecast that obesity may shave up to five years off average life spans in coming decades.

And yet a number of scholars have accused obesity experts, public health officials and the media of exaggerating the health

HUGH KRETSCHMER

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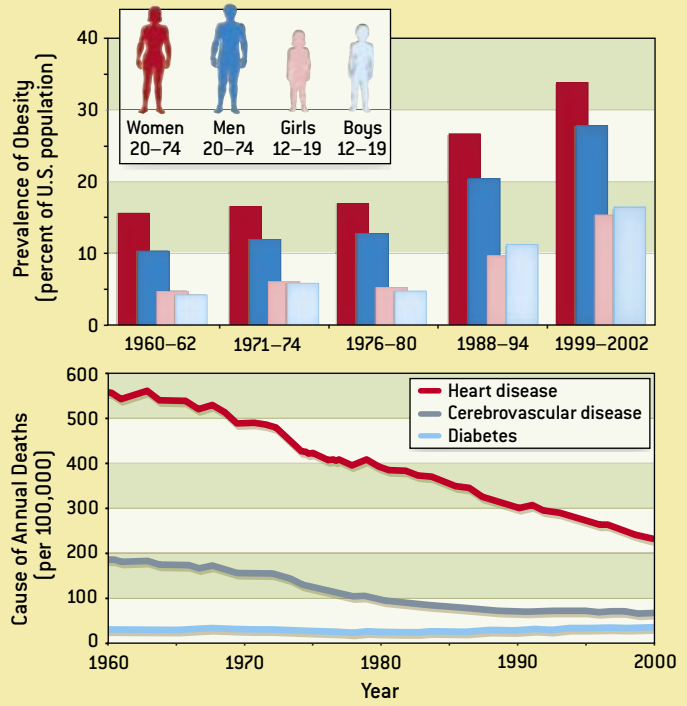
How Fatal Is Fat?



PREVALENCE OF OBESITY has roughly doubled in the U.S. since 1980 among adults and has tripled among children (*top*). Although deaths caused by diabetes have risen somewhat, predicted increases in mortality from heart disease and stroke have not materialized (*bottom*).

effects of the epidemic of overweight and obesity. The charges appear in a recent flurry of scholarly books, including *The Obesity Myth,* by Paul F. Campos (Gotham Books, 2004); *The Obesity Epidemic: Science, Morality and Ideology,* by Michael Gard and Jan Wright (Routledge, 2005); *Fat Politics: The Real Story behind America's Obesity Epidemic,* by J. Eric Oliver (Oxford University Press, 2005); and *The Gospel of Food: Everything You Think You Know about Food Is Wrong,* by Barry Glassner (Ecco/HarperCollins, 2007).

These critics, all academic researchers outside the medical community, do not dispute surveys that find the obese fraction of the population to have roughly doubled in the U.S. and many parts of Europe since 1980. And they acknowledge that obesity, especially in its extreme forms, does seem to be a factor in some illnesses and premature deaths.

They allege, however, that experts are blowing hot air when they warn that overweight and obesity are causing a massive, and worsening, health crisis. What is really going on, asserts Oliver, a political scientist at the University of Chicago, is that "a relatively small group of scientists and doctors, many directly funded by the weight-loss industry, have created an arbitrary and unscientific definition of overweight and obesity. They have inflated claims and distorted statistics on the consequences of our growing weights, and they have largely ignored the complicated health realities associated with being fat."

One of those complicated realities, concurs Campos, a professor of law at the University of Colorado at Boulder, is the widely accepted evidence that genetic differences account for 50 to 80 percent of the variation in fatness within a population. Because no safe and widely practical methods have been shown to induce long-term loss of more than about 5 percent of body weight, Campos says, "health authorities are giving people advice—maintain a body mass index in the 'healthy weight' range—that is literally impossible for many of them to follow." Body mass index, or BMI, is a weight-to-height ratio [*see top box on opposite page for the definition of weight categories*].

By exaggerating the risks of fat and the feasibility of weight loss, Campos and Oliver claim, the Centers for Disease Control and Prevention, the U.S. Department of Health and Human Services and the World Health Organization inadvertently perpetuate stigma, encourage unbalanced diets and, perhaps, even exacerbate weight gain. "The most perverse irony is that we may be creating a disease simply by labeling it as such," Campos states.

A Body to Die For

ON FIRST HEARING, these dissenting arguments may sound like nonsense. "If you really look at the medical literature and think obesity isn't bad, I don't know what planet you are on," says James O. Hill, an obesity researcher at the University of Colorado Health Sciences Center. Dietary guidelines issued by the DHHS and the U.S. Department of Agriculture in January 2005 state confidently that "a high prevalence of overweight and obesity is of great public health concern because excess body fat leads to a higher risk for premature death, type 2 diabetes, hypertension, dyslipidemia [high cholesterol], cardiovascular disease, stroke, gall bladder disease, respiratory dysfunction, gout, osteoarthritis, and certain kinds of cancers." The clear implication is that any degree of overweight is dangerous and that a high BMI is not merely a marker of high risk but a cause.

"These supposed adverse health consequences of being

OVERVIEW
A CRISIS IN QUESTION

- According to conventional wisdom, excess fat is an important cause of chronic disease, and the epidemic increase in obesity portends a coming health crisis.
- Four recent books by academic researchers argue that in fact the consequences of this trend for public health remain far less certain—and almost certainly less dire—than commonly suggested by obesity experts, government authorities and media reports.

LUCY READING-IKKANDA; SOURCES: *HEALTH, UNITED STATES, 2004,* U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; *STATISTICAL ABSTRACT OF THE UNITED STATES: 2004–2005,* U.S. CENSUS BUREAU

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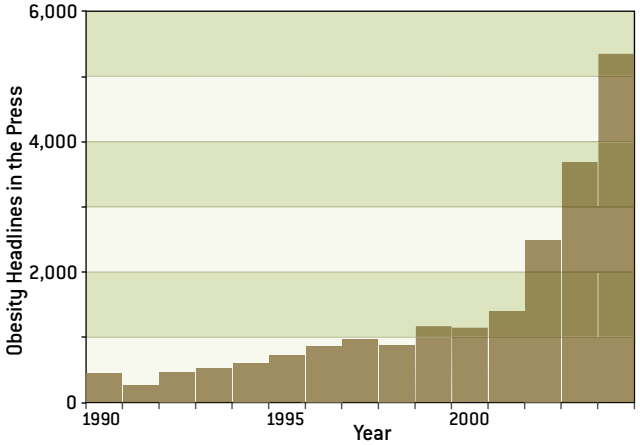
'overweight' are not only exaggerated but for the most part are simply fabricated," Campos alleges. Surprisingly, a careful look at recent epidemiological studies and clinical trials suggests that the critics, though perhaps overstating some of their accusations, may be onto something.

Oliver points to a recent and unusually thorough analysis of three large, nationally representative surveys, for example, that found only a very slight—and statistically insignificant—increase in mortality among mildly obese people, as compared with those in the healthy weight category, after subtracting the effects of age, race, sex, smoking and alcohol consumption. The three surveys—medical measurements collected in the early 1970s, late 1970s and early 1990s, with subjects matched against death registries nine to 19 years later—indicate that it is much more likely that U.S. adults who fall in the overweight category have a *lower* risk of premature death than do those of so-called healthy weight. The overweight segment of the "epidemic of overweight and obesity" is more likely reducing death rates than boosting them. "The majority of Americans who weigh too much are in this category," Campos notes.

Counterintuitively, "underweight, even though it occurs in only a tiny fraction of the population, is actually associated with more excess deaths than class I obesity," says Katherine M. Flegal, a senior research scientist at the CDC. Flegal led the study, which appeared in the *Journal of the American Medical Association* in 2005 after undergoing four months of scrutiny by internal reviewers at the CDC and the NCI and additional peer review by the journal.

These results contradicted two previous estimates that were the basis of the oft-repeated claim that obesity cuts short 300,000 or more lives a year in the U.S. There are good reasons to suspect, however, that both these earlier estimates were compromised by dubious assumptions, statistical errors and outdated measurements [*see box on page 81*].

When Flegal and her co-workers analyzed just the most recent survey, which measured heights and weights from 1988 to 1994 and deaths up to 2000, even severe obesity failed to show up as a statistically significant mortality risk. It seems probable, Flegal speculates, that in recent decades improvements in medical care have reduced the mortality level associated with obesity. That would square, she observes, with both the unbroken rise in life expectancies and the uninterrupted fall in death rates attributed to heart disease and stroke throughout the entire 25-year spike in obesity in the U.S.



LUCY READING-IKKANDA; SOURCE: LEXIS-NEXIS, ADJUSTED FOR CHANGES IN DATABASE CONTENTS FOR 1990–2003

MEDIA STORIES on obesity are exploding in number, but Michael Gard and Jan Wright, authors of *The Obesity Epidemic: Science, Morality and Ideology,* charge the media with oversimplifying research results in ways that reinforce public prejudices and superstitions about body weight.

A Disease by Definition

U.S. federal policy and WHO guidelines assign weight categories according to body mass index, or BMI, using the following formula and table:

$$\text{BMI} = \frac{(\text{weight in kilograms})}{(\text{height in meters})^2}$$

Below 18.5	18.5 to 24.9	25 to 29.9	30 to 34.9	35 to 39.9	40 or over
Underweight	Healthy weight	Overweight	Mild (class I) obesity	Moderate (class II) obesity	Severe (class III) obesity

Weighing the Evidence

BUT WHAT ABOUT the warning by Olshansky and Allison that the toll from obesity is yet to be paid, in the form of two to five years of life lost? "These are just back-of-the-envelope, plausible scenarios," Allison hedges, when pressed. "We never meant for them to be portrayed as precise." The life expectancy costs were based on a handful of convenient but dubious assumptions. And although most media reports jumped on the "two to five years" quote, very few mentioned that the paper offered no statistical analysis to back it up.

The August 2006 retiree study, led by Kenneth F. Adams of the NCI, was widely reported as supporting the lethal risks of being moderately overweight. Yet Adams's results actually mirrored Flegal's closely. After controlling for the influence of smoking, drinking, physical activity, education, age, race and gender, the NCI-led group found that death rates were far higher for the underweight than for the obese. And on average, overweight men and women died at a lower rate than those in the healthy weight range. Men with BMIs between 25 and 28 tended to live longest, whereas a broader sweet spot for women extended from 21 to 28.

The researchers used questionnaires rather than scales to gather their data, and they did not correct for the known tendency of obese people to lie about their weights, thus lumping themselves into the overweight category. All the nearly 530,000 subjects were members of the American Association of Retired Persons and hence older, wealthier and more educated than the populace at large.

So some scientists were skeptical of the paper's overall conclusion that overweight increases mortality—an hypothesis supported only by a subanalysis limited to the roughly one

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Experts agree that severe obesity can shorten your life, but there is less agreement on the health effects of being moderately overweight.

fifth of the subjects who had never smoked and who had been able to recall what they weighed when they were age 50.

Critics decry episodes such as this one as egregious examples of a general bias in the obesity research community. Medical researchers tend to cast the expansion of waistlines as an impending disaster "because it inflates their stature and allows them to get more research grants. Government health agencies wield it as a rationale for their budget allocations," Oliver writes. (The NIH increased its funding for obesity research by 10 percent in 2005, to $440 million.) "Weight-loss companies and surgeons employ it to get their services covered by insurance," he continues. "And the pharmaceutical industry uses it to justify new drugs."

"The war on fat," Campos concurs, "is really about making some of us rich." He points to the financial support that many influential obesity researchers receive from the drug and diet industries. Allison, a professor at the University of Alabama at Birmingham, discloses payments from 148 such companies, and Hill says he has consulted with some of them as well. (Federal policies prohibit Flegal and other CDC scientists from accepting nongovernmental wages.) None of the dissenting authors cites evidence of anything more than a potential conflict of interest, however.

Is Fat Good for the Old?

"A lot of data suggest that the effect of obesity on mortality is less strong for old people than it is for young people," says Katherine M. Flegal of the CDC. "Some studies suggest that a high BMI is not a major risk factor among the elderly. Having a nutritional reserve seems to make people more resilient if they are hospitalized. So when you make estimates of deaths from obesity, it is very important which estimates you use for the oldest group. Obesity might be a tremendous risk factor in young people, but their death rates are very low."

RONNIE KAUFMAN *Corbis*

Those Confounded Diseases

EVEN THE BEST mortality studies provide only a flawed and incomplete picture of the health consequences of the obesity epidemic, for three reasons. First, by counting all lives lost to obesity, the studies so far have ignored the fact that some diversity in human body size is normal and that every well-nourished population thus contains some obese people. The "epidemic" refers to a sudden increase in obesity, not its mere existence. A proper accounting of the epidemic's mortal cost would estimate only the number of lives cut short by whatever amount of obesity exceeds the norm.

Second, the analyses use body mass index as a convenient proxy for body fat. But BMI is not an especially reliable stand-in. And third, although everyone cares about mortality, it is not the only thing that we care about. Illness and quality of life matter a great deal, too.

All can agree that severe obesity greatly increases the risk of numerous diseases, but that form of obesity, in which BMI exceeds 40, affects only about one in 12 of the roughly 130 million American adults who set scales spinning above the "healthy" range. At issue is whether rising levels of overweight, or of mild to moderate obesity, are pulling up the national burden of heart disease, cancer and diabetes.

In the case of heart disease, the answer appears to be no—or at least not yet. U.S. health agencies do not collect annual figures on the incidence of cardiovascular disease, so researchers look instead for trends in mortality and risk factors, as measured in periodic surveys. Both have been falling.

Alongside Flegal's April 2005 paper in *JAMA* was another by Edward W. Gregg and his colleagues from the CDC that found that in the U.S. the prevalence of high blood pressure dropped by half between 1960 and 2000. High cholesterol followed the same trend—and both declined more steeply among the overweight and obese than among those of healthy weight. So although high blood pressure is still twice as common among the obese as it is among the lean, the paper notes that "obese persons now have better [cardiovascular disease] risk profiles than their leaner counterparts did 20 to 30 years ago."

The findings reinforce those published in 2001 by a 10-year WHO study that examined 140,000 people in 38 cities on four continents. The investigators, led by Alun Evans of the Queen's University of Belfast, saw broad increases in BMI and equally broad declines in high blood pressure and high

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Mortal Mistakes

Media coverage of the obesity epidemic surged in 1999 following a report in the *Journal of the American Medical Association* by David B. Allison and others that laid about 300,000 annual deaths in the U.S. at the doorstep of obesity. The figure quickly acquired the status of fact in both the popular press and the scientific literature, despite extensive discussion in the paper of many uncertainties and potential biases in the approach that the authors used.

Like election polls, these estimates involve huge extrapolations from relatively small numbers of actual measurements. If the measurements—in this case of height, weight and death rates—are not accurate or are not representative of the population at large, then the estimate can be far off the mark. Allison drew statistics on the riskiness of high weights from six different studies. Three were based on self-reported heights and weights, which can make the overweight category look riskier than it really is (because heavy people tend to lie about their weight). Only one of the surveys was designed to reflect the actual composition of the U.S. population. But that survey, called NHANES I, was performed in the early 1970s, when heart disease was much more lethal than it is today. NHANES I also did not account as well for participants' smoking habits as later surveys did.

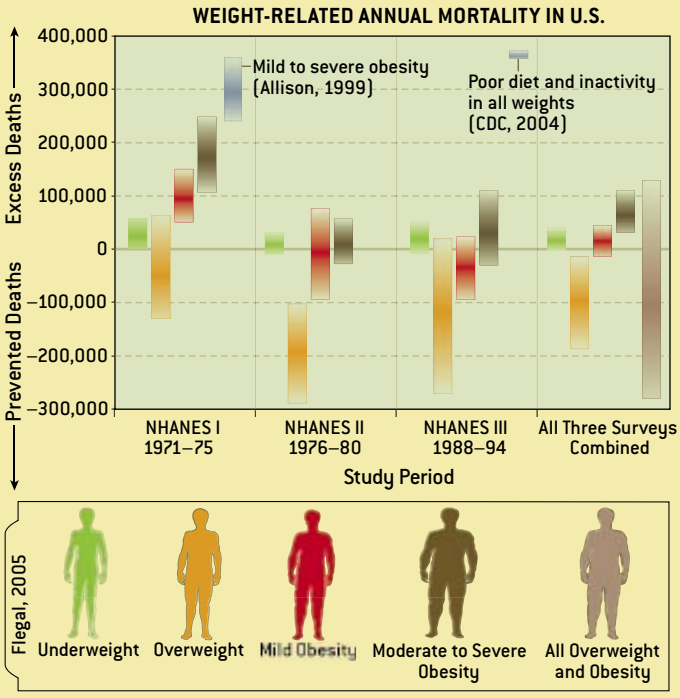
That matters because smoking has such a strong influence on mortality that any problem in subtracting its effects could distort the true mortal risks of obesity. Allison and his colleagues also used an incorrect formula to adjust for confounding variables, according to statisticians at the CDC and the National Cancer Institute.

Perhaps the most important limitation noted in the 1999 paper was its failure to allow the mortality risk associated with a high BMI to vary—in particular, to drop—as people get older [*see box on opposite page*].

Surprisingly, none of these problems was either mentioned or corrected in a March 2004 paper by CDC scientists, including the agency's director, that arrived at a higher estimate of 400,000 deaths using Allison's method, incorrect formula and all. Vocal criticism led to an internal investigation at the CDC; in January 2005 the authors published a "corrected" estimate of 365,000 obesity-related deaths a year, which they labeled as stemming from "poor diet and inactivity." The new figure corrected only data-entry mistakes, however.

In April 2005 another CDC scientist, Katherine M. Flegal, published a new and much improved estimate based entirely on nationally representative surveys that actually measured weights and heights. Flegal's analysis allows for risks that vary with age and claims to correct properly for confounding factors. But "the biggest reason that we get different results is that we used newer data," she asserts.

As illustrated in the chart below, the new analysis suggests that it is still far from certain whether there is any measurable mortality toll at all among overweight and obese Americans as a group. Even among the moderately and severely obese (those whose BMI exceeds 35), the plausible annual mortality found in the 1988–1994 survey ranges from 122,000 extra to 7,000 fewer deaths than one would expect based on the death rates of "healthy weight" people. —*W.W.G.*



cholesterol. "These facts are hard to reconcile," they wrote.

It may be, Gregg suggests, that better diagnosis and treatment of high cholesterol and blood pressure have more than compensated for any increases from rising obesity. It could also be, he adds, that obese people are getting more exercise than they used to; regular physical activity is thought to be a powerful preventative against heart disease.

Oliver and Campos explore another possibility: that fatness is partially—or even merely—a visible marker of other factors that are more important but harder to perceive. Diet composition, physical fitness, stress levels, income, family history and the location of fat within the body are just a few of 100-odd "independent" risk factors for cardiovascular disease identified in the medical literature. The observational studies that link obesity to heart disease ignore nearly all of them and in doing so effectively assign their causal roles to obesity. "By the same criteria we are blaming obesity for heart disease," Oliver writes, "we could accuse smelly clothes, yellow teeth or bad breath for lung cancer instead of cigarettes."

LUCY READING-IKKANDA; SOURCES: NATIONAL CENTER FOR HEALTH STATISTICS; *JAMA*, VOL. 282, PAGE 1530; OCTOBER 27, 1999, AND VOL. 291, PAGE 1238; MARCH 10, 2004

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As for cancer, a 2003 report on a 16-year study of 900,000 American adults found significantly increased death rates for several kinds of tumors among overweight or mildly obese people. Most of these apparently obesity-related cancers are very rare, however, killing at most a few dozen people a year for every 100,000 study participants. Among women with a high BMI, both colon cancer and postmenopausal breast cancer risks were slightly elevated; for overweight and obese men, colon and prostate cancer presented the most common increased risks. For both women and men, though, being overweight or obese seemed to confer significant *protection* against lung cancer, which is by far the most commonly lethal malignancy. That relation held even after the effects of smoking were subtracted [*see box below*].

Obesity's Catch-22

IT IS THROUGH type 2 diabetes that obesity seems to pose the biggest threat to public health. Doctors have found biological connections between fat, insulin, and the high blood sugar levels that define the disease. The CDC estimates that 55 percent of adult diabetics are obese, significantly more than the 31 percent prevalence of obesity in the general population. And as obesity has become more common, so, too, has diabetes, suggesting that one may cause the other.

Yet the critics dispute claims that diabetes is soaring (even among children), that obesity is the cause, and that weight loss is the solution. A 2003 analysis by the CDC found that "the prevalence of diabetes, either diagnosed or undiagnosed, and of impaired fasting glucose did not appear to increase substantially during the 1990s," despite the sharp rise in obesity.

"Undiagnosed diabetes" refers to people who have a single positive test for high blood sugar in the CDC surveys. (Two or more positive results are required for a diagnosis of diabetes.) Gregg's paper in April reiterates the oft-repeated "fact" that for every five adults diagnosed with diabetes, there are three more diabetics who are undiagnosed. "Suspected diabetes" would be a better term, however, because the single test used by the CDC may be wildly unreliable.

In 2001 a French study of 5,400 men reported that 42 percent of the men who tested positive for diabetes using the CDC method turned out to be nondiabetic when checked by a "gold standard" test 30 months later. The false negative rate—true diabetics missed by the single blood test—was just 2 percent.

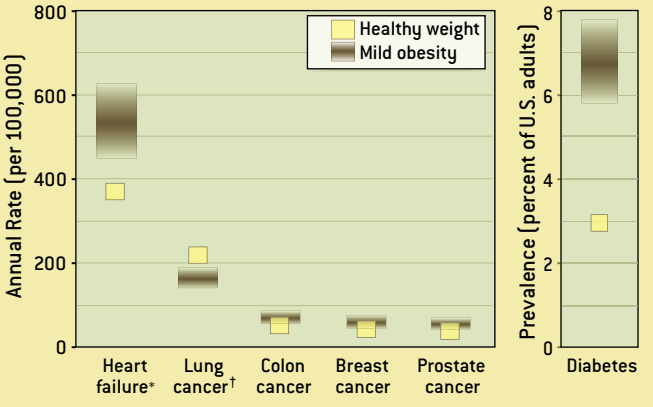
But consider the growing weights of children, Hill urges.

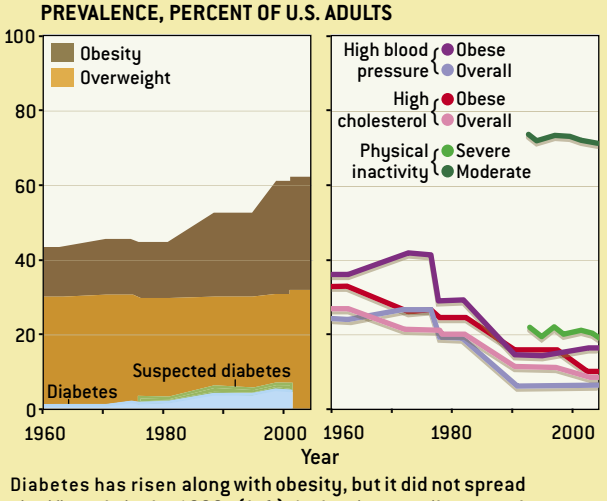
Obesity and Illness

Mild and moderate obesity seem in some studies to elevate risks of several serious diseases (*right*). Yet the trends in these diseases (*below* and *bottom right*) reveal no simple connection between the epidemic rise in obesity and public health in the U.S.

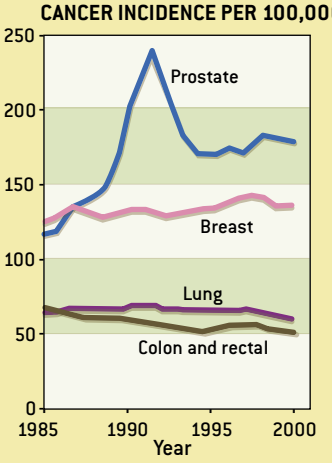
* Rate for heart failure includes all obesity (BMI >30)

† Rates for cancers represent mortality; lung and colon cancer in men only





Diabetes has risen along with obesity, but it did not spread significantly in the 1990s (*left*). And major contributors to heart disease have fallen in recent decades (*right*).



Incidence of cancers linked to obesity (*left*) also paints a complicated picture. New diagnoses of colon and of lung cancer have fallen slightly. (Fatness may actually protect against some lung cancer.) The upward trend in diagnosis of breast and prostate tumors may be a result mainly of increased screening for these diseases, as more sensitive and affordable tests catch tumors that previously escaped detection.

LUCY READING-IKKANDA; SOURCES: *INTERNATIONAL JOURNAL OF OBESITY*, VOL. 26, PAGE 1050 (*heart failure*); *NEJM*, VOL. 348, PAGES 1625–1638 (*cancer mortality*); *JAMA*, VOL. 293, PAGE 1871 (*diabetes*); *JAMA*, VOL. 288, PAGE 1724, VOL. 291, PAGE 2847, AND *HEALTH, UNITED STATES, 2004* (*obesity and overweight*); *DIABETES CARE*, VOL. 27, PAGE 2809 (*diabetes trend*); *JAMA*, VOL. 293, PAGE 1871 (*blood pressure and cholesterol*); CDC BEHAVIORAL RISK FACTOR SURVEILLANCE SYSTEM (*physical activity*); NATIONAL CANCER INSTITUTE (*cancer incidence*)

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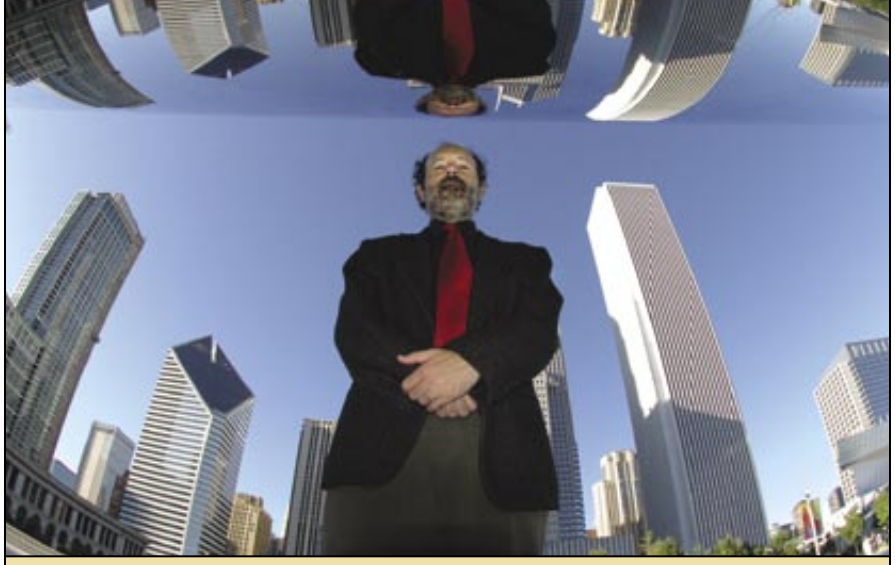

DISTORTED VIEWS of medical research largely fuel the public's anxiety about the obesity epidemic, claims Paul F. Campos, author of *The Obesity Myth.* He castigates health authorities for a "constant barrage of scientifically baseless propaganda" about the risks of fat.

"You're getting kids at 10 to 12 years of age developing type 2 diabetes. Two generations ago you never saw a kid with it."

Anecdotal evidence often misleads, Campos responds. He notes that when CDC researchers examined 2,867 adolescents in the NHANES survey of 1988–1994, they identified just four that had type 2 diabetes. A more focused study in 2003 looked at 710 "grossly obese" boys and girls ages six to 18 in Italy. These kids were the heaviest of the heavy, and more than half had a family history (and thus an inherited risk) of diabetes. Yet only one of the 710 had type 2 diabetes.

Nevertheless, as many as 4 percent of U.S. adults might have diabetes because of their obesity—if fat is in fact the most important cause of the disease. "But it may be that type 2 diabetes causes fatness," Campos argues. (Weight gain is a common side effect of many diabetes drugs.) "A third factor could cause both type 2 diabetes and fatness." Or it could be some complex combination of all these, he speculates.

Large, long-term experiments are the best way to test causality, because they can alter just one variable (such as weight) while holding constant other factors that could confound the results. Obesity researchers have conducted few of these so-called randomized, controlled trials. "We don't know what happens when you turn fat people into thin people," Campos says. "That is not some oversight; there is no known way to do it"—except surgeries that carry serious risks and side effects.

"About 75 percent of American adults are trying to lose or maintain weight at any given time," reports Ali H. Mokdad, chief of the CDC's behavioral surveillance branch. A report in February 2005 by Marketdata Enterprises estimated that in 2004, 71 million Americans were actively dieting and that the nation spent about $46 billion on weight-loss products and services.

Dieting has been rampant for many years, and bariatric surgeries have soared in number from 36,700 in 2000 to roughly 140,000 in 2004, according to Marketdata. Yet when Flegal and others examined the CDC's most recent follow-up survey in search of obese senior citizens who had dropped into a lower weight category, they found that just 6 percent of non-obese, older adults had been obese a decade earlier.

Campos argues that for many people, dieting is not merely ineffective but downright counterproductive. A large study of nurses by Harvard Medical School doctors reported in 2004 that 39 percent of the women had dropped weight only to regain it; those women later grew to be eight pounds heavier on average than women who did not lose weight.

Weight-loss advocates point to two trials that in 2001 showed a 58 percent reduction in the incidence of type 2 diabetes among people at high risk who ate better and exercised more. Participants lost little weight: an average of 2.7 kilograms after two years in one trial, 5.6 kilograms after three years in the other.

"People often say that these trials proved that weight loss prevents diabetes. They did no such thing," comments Steven N. Blair, an obesity researcher who heads the Cooper Institute in Dallas. Because the trials had no comparison group that simply ate a balanced diet and exercised without losing weight, they cannot rule out the possibility that the small drop in subjects' weights was simply a side effect. Indeed, one of the trial groups published a follow-up study in January 2005 that concluded that "at least 2.5 hours per week of walking for exercise during follow-up seemed to decrease the risk of diabetes by 63 to 69 percent, largely independent of dietary factors and BMI."

"H. L. Mencken once said that for every complex problem there is a simple solution—and it's wrong," Blair muses. "We have got to stop shouting from the rooftops that obesity is bad for you and that fat people are evil and weak-willed and that the world would be lovely if we all lost weight. We need to take a much more comprehensive view. But I don't see much evidence that that is happening." SA

W. Wayt Gibbs, a contributing editor at Scientific American, *is executive editor of Intellectual Ventures in Bellevue, Wash. Founded in 2000, the company conceives, acquires, patents and licenses inventions.*

MORE TO EXPLORE

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Secular Trends in Cardiovascular Disease Risk Factors according to Body Mass Index in US Adults. Edward W. Gregg in *Journal of the American Medical Association,* Vol. 293, pages 1868–1874; April 20, 2005.

MARC POKEMPNER

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ANOREXIA NERVOSA affects many young women, such as this patient in the eating disorders clinic at the New York State Psychiatric Institute, a part of Columbia-Presbyterian Medical Center.

ABRAHAM MENASHE

Dying to Be Thin

Eating disorders cripple—literally—millions of young women, in large part because treatments are not always effective or accessible

by **Kristin Leutwyler**

I don't own a scale. I don't trust myself to have one in the house—maybe in the same way that recovered alcoholics rightfully clear their cabinets of cold medicines and mouthwash. At 5′7″, I know that I usually weigh 125 pounds, and I know that is considered normal for my frame. But 22 years ago, when I was 15 years old and the same height, I weighed 67 pounds, and I thought I was grossly, repulsively obese.

My own bout with anorexia nervosa—the eating disorder that made me starve myself into malnutrition—was severe but short-lived. I had a wonderful physician who worked hard to earn my trust and safeguard my health. And I had

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one great friend who slowly, over many months, proved to me that one ice cream cone wouldn't make me fat nor would being fat make me unlovable. A year later I was back up to 95 pounds. I was still scrawny, but at least I knew it.

I was—am—lucky. Eating disorders are often chronic and startlingly common. One percent of all teenage girls suffer from anorexia nervosa at some point. Two to 3 percent develop bulimia nervosa, a condition in which sufferers consume large amounts of food only to then "purge" away the excess calories by making themselves vomit, by abusing laxatives and diuretics, or by exercising obsessively. And binge eaters—who overeat until they are uncomfortably full—make up another 2 percent of the population. Since the 1960s the incidence of eating disorders has doubled, and clinicians are seeing an increasing number of cases among preadolescents, women older than 30, nonwhites and men.

In addition to the mental pain these illnesses cause sufferers and their families and friends, they also have devastating physical consequences. In the most serious cases, binge eating can rupture the stomach or esophagus. Purging can flush the body of vital minerals, causing cardiac arrest. Self-starvation can also lead to heart failure. Among anorexics, who undergo by far the worst complications, the mortality rate after 10 years is 6.6 percent, reports Katherine A. Halmi, professor of psychiatry at Weill Cornell Medical College and director of the Westchester-based Eating Disorders Program of New York–Presbyterian Hospital. After 30 years of struggling with the condition, nearly one fifth die.

Because studies clearly show that people who recover sooner are less likely to relapse, the push continues to discover better treatments. Eating disorders are exceedingly complex diseases, brought on by a mix of environmental, social and biological factors. And the current prognosis is grim. Among anorexics, only one quarter make a full recovery; for bulimics, the statistic is only one half. In recent years, however, scientists have made some small advances. Various forms of therapy are proving beneficial, and some medications—among them the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs)—are helping certain patients. "SSRIs are not wonder drugs for eating disorders," says Robert I. Berkowitz of the University of Pennsylvania. "But treatments have become more successful, and so we're feeling hopeful, even though we have a long way to go to understand these diseases."

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Weighing the Risks

WHEN I BEGAN working on this article, I phoned my former physician, a specialist in adolescent medicine, and I was a little surprised that she remembered my name but not my diagnosis. In all fairness, my illness was a textbook case. I had faced many common risk factors, starting with a "fat list" on the bulletin board at my ballet school. The list named girls who needed to lose weight and by how much. I was never on it. But the possibility filled me with so much dread that at the start of the summer, I decided I had to get into better shape. I did sit-ups and ran every day before and after ballet classes. I stopped eating sweets, fats and meat. And when I turned 15 in September, I was as lean and strong as I've ever been.

Scientists know that environment contributes heavily to the development of eating disorders. Many anorexic and bulimic women are involved in ballet, modeling or some other activity that values low body weight. Men with eating disorders often practice sports that emphasize dieting and fasting, such as wrestling and track. And waiflike figures in fashion and the media clearly hold considerable sway. "The cultural ideal for beauty for women has become increasingly thin over the years," Berkowitz notes. Among the millions now affected by eating disorders every year, more than 90 percent are female.

Like me, most young women first develop an eating disorder as they near puberty. "Girls start to plump up at puberty," says Estherann M. Grace of Children's Hospital in Boston. "And this is also when they start looking at magazines and thinking, 'What's wrong with me?' " Recognizing that anorexia nervosa often arises as girls begin to mature physically, psychiatrists have revised the diagnostic standards. "It used to be that one of the criteria was that you had to have missed a period or suffered from amenorrhea for three months," says Marcie B. Schneider of Greenwich Hospital in Connecticut. "And so we missed all those kids with eating disorders who had not yet reached puberty or had delayed it." Now the criteria include a failure to meet expected growth stages, and more 10-, 11- and 12-year-olds are being diagnosed.

Puberty is a stressful time—and stressful events typically precede the onset of psychiatric conditions, including eating disorders. Maybe I would have stopped dieting had my parents not separated in the summer, or had my grandmother not died that fall, or had I not spent my entire winter vacation dancing 30-odd performances of the *Nutcracker*. Maybe. I do know that as my life spun out of control around me, my diet became the one thing I felt I

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could still rein in. "Anorexics are terribly fearful of a loss of control," Grace says, "and eating gives them one area in which they feel they have it."

Most people under stress will overeat or undereat, Grace adds, but biology and personality types make some more vulnerable to extremes. Anorexics tend to be good students, dedicated athletes and perfectionists—and so it makes some sense that in dieting, too, they are highly disciplined. In contrast, bulimics and binge eaters are typically outgoing and adventurous, prone to impulsive behaviors. And all three illnesses frequently arise in conjunction with depression, anxiety and obsessive-compulsive disorder—conditions that tend to run in families and are related to malfunctions in the system regulating the neurotransmitter serotonin.

I most definitely became obsessed. I read gourmet magazines cover to cover, trying to imagine the taste of foods I would not let myself have—ever. I cut my calories back to 800 a day. I counted them down to the singles in a diet soda. I measured and weighed my food to make my tally more accurate. And I ate everything I dished, to make sure I knew the precise number of calories I had eaten. By November, none of my clothes fit. When I sat, I got bruises where my hip bones jutted out in the back. My hair thinned, and my nails became brittle. I was continuously exhausted, incredibly depressed and had no intention of quitting. It felt like a success.

Sitting Down for Treatment

THE FIRST BARRIER to treating eating disorders is getting people to admit that they have one. Because bulimics are often a normal weight and hide their strange eating rituals, they can be very hard to identify. Similarly, binge eaters are extremely secretive about their practices. And even though seriously ill anorexics are quite noticeably emaciated, they are the least willing of all patients with eating disorders to get help. "Anorexics are not motivated for treatment in the same way as bulimics are," Halmi comments. "Because anorexia gives patients a sense of control, it is seen as a positive thing in their lives, and they're terrified to give that up."

I certainly was—and a large part of getting better involved changing that way of thinking. To that end, cognitive behavioral therapy (CBT) has had fair success in treating people with anorexia, bulimia and binge eating disorder. "There are three main components," explains Halmi, who views CBT as one of the most effective treatments. Patients keep diaries of what they eat, how they feel when they eat and what events, if any, prompt them to eat. I used to feel guilty before meals and would ask my mother for permission before I ate. She never would have denied me, but asking somehow lessened my guilt.

CBT also helps patients identify flawed perceptions (such as thinking they are fat) and, with the aid of a therapist, list evidence for and against these ideas and then try to correct them. This process let me eventually see the lack of reason in my belief that, say, a single cookie would lure me into a lifetime bender of reckless eating and obesity. And CBT patients work through strategies for handling situations that reinforce their abnormal perceptions. I got rid of my scale and avoided mirrors.

Working in collaboration with researchers at Stanford University, the University of Minnesota and the University of North Dakota, Halmi has compared relapse rates in anorexics who have been randomly assigned to treatment with CBT or the SSRI drug Prozac, or a combination of both. Among those receiving only Prozac, 66 percent dropped out of the study, leading the researchers to conclude that most anorexics will not benefit from medication alone. Among those who received both Prozac and CBT, however, roughly half finished the course of treatment. And compared with those participants who received only CBT, the drug did seem to boost the effectiveness of the therapy. In practice, the antihistamine Cyproheptadine can also facilitate weight gain in certain patients, and tranquilizers can sometimes help those who are very agitated or who exercise obsessively.

For patients with bulimia, SSRIs also appear to be effective adjuncts when CBT alone does not help. In conjunction with James Mitchell, director of neuroscience at the University of North Dakota, and Scott J. Crow, professor of psychiatry at the University of Minnesota, Halmi collected data on 100 bulimics who received cognitive behavioral therapy for four months. Those who still did not improve underwent further therapy and drug treatment with Prozac. "When it comes to

BERNAT ARMANGUE *AP Photo*

MODEL showed off a design by Locking Shocking during the Pasarela Cibeles fashion show in 2005. One year later, Spain's top fashion show turned away some models because they were too thin. Only models with a body mass index over 18 were allowed on the Madrid catwalks, and 30 percent of the women flunked, according to the Association of Fashion Designers of Spain.

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bulimia," Berkowitz tells me, "it is clear that both psychotherapy and pharmacology are helpful."

Swallowing the Truth

NEW TREATMENTS for eating disorders could benefit millions of adolescents—if they can get them. Most face a greater challenge getting help today than I did 22 years ago. "One of the big topics now is how to survive in this era of managed care," Schneider tells me. "You have to be at death's door to get into a psychiatric hospital," Berkowitz says, "and once a patient is stabilized, the reimbursements often stop. This is not an inexpensive disease to have." I went through a year of weekly therapy before I reached a stable, if not wholly healthy, weight. In comparison, Berkowitz notes that the insurance policies he has encountered recently often pay for only 20 sessions, with the patient responsible for a 50 percent co-payment.

"It's absolutely sinful," Halmi says. "It is a disaster for eating-disorder patients, particularly anorexics." She points out that relapse rates are much lower in adolescents who receive treatment long enough to get back up to 90 percent of their ideal weight; those who gain less typically fare worse. But insurance rarely lasts long enough. "It used to be you could hospitalize a kid for three or four months," Schneider says. "Now you can at most get a month or so, and it's on a case-by-case basis. You're fighting with the insurance company every three days." The fact that it may be cheaper to treat these patients right the first time seems to make little difference to health insurers, she adds: "Their attitude is that these kids will probably have a different carrier down the road."

Down the road, the consequences of inadequate treatment are chilling. Debra K. Katzman of the Hospital for Sick Children in Toronto has taken magnetic resonance imaging (MRI) scans of young women with anorexia nervosa before and after recovery and found that the volume of cerebral gray and white matter in their brains seemed to have decreased. "The health of these kids does rapidly improve when they gain back some weight," Schneider says, "but the changes on the MRIs do not appear to go away." Indeed, the gray matter deficits persist.

In addition, those who do not receive sufficient nutrition during their teen years seriously damage their skeletal growth. "The bones are completed in the second decade, right when this disease hits, so it sets people up for long-term problems," Grace asserts. These problems range from frequent fractures to thinning bones and premature osteoporosis. "I talked to one girl today who is 16. She hasn't been underweight for that long, but already she is lacking 25 percent of the bone density normal for kids her age," Schneider says. "And I have to explain to her why she has to do what no inch in her wants to—eat—so that she won't be in a wheelchair at age 50."

Because drugs used to treat bone loss in adults do nothing in teens, researchers are looking for ways to remedy this particular symptom. "[Loss of bone is] related to their not menstruating and not having estrogen," Grace explains. "But whereas estrogen does protect older women against bone loss, it doesn't seem to help younger ones." She and a co-worker are now testing the protective effects of another hormone in young girls. Halmi also emphasizes that estrogen treatment for patients with eating disorders is a waste of time. Instead "you want to get them back up to a normal weight," she states, "and let the body start building bone itself."

All of which brings us back to the concept of normal weight—something many women simply don't want to be. A 1996 study found that even centerfold models feel the need to lie about their heights and weights. Christopher P. Szabo, now at the University of the Witwatersrand in Johannesburg, reviewed the reported measurements of women in South African editions of *Playboy* between February 1994 and February 1995 and calculated their apparent body mass indices. Even though these models all looked healthy, 72 percent had claimed heights and weights that gave them a body mass index below 18—the medical cutoff for malnourishment.

More recently, Peter T. Katzmarzyk, now at Queen's University in Canada, and Caroline Davis of York University in Toronto surveyed the weight and measurements of *Playboy* centerfolds from 1978 to 1998. Again they found a significant decrease over time, with 75 percent of the women reporting measurements that would put them at less than 85 percent of their ideal weight. "Maybe 5 percent of the population could achieve an 'ideal' figure, with surgical help," Grace jokes. "I'm sorry, but Barbie couldn't stand upright if she weren't plastic."

Barbie also could not work Madrid's fashion week. Setting an important precedent, the local government that sponsors the show enforced the world's first ban on overly thin models in September. Only models having a BMI over 18 were allowed onto the catwalks. Although the ban drew fire from several modeling agencies and designers, Britain's culture minister and Milan's mayor have called for similar rules at their own events.

Shifting the image of ideal beauty back toward a healthier weight can only help. I remember all too well thinking that I would look fat at a normal weight. Sometimes I still do worry that I look fat, but I take my perceptions with a grain of salt. And fortunately, I no longer measure my self-worth in pounds—or the lack thereof. SA

Brain scans of young women with anorexia nervosa found that the volume of gray and white matter seemed to have decreased.

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